FDA Executive Summary

Prepared for the
March 12, 2010 meeting of the
Neurologic Devices Panel

P960009/S068
Medtronic, Inc.
Deep Brain Stimulation System for Epilepsy

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1. Introduction

This is FDA's Executive Summary of premarket approval (PMA) application P960009/S068 from Medtronic, Inc. for the Deep Brain Stimulation (DBS) System for Epilepsy. This summary contains a brief device description and a summary of the clinical study conducted by the sponsor. The sponsor bases its request for approval of the neurostimulation system on the results of this study and has proposed the following indication:

> "Bilateral anterior thalamic nucleus stimulation using the Medtronic DBS System for Epilepsy is indicated as adjunctive therapy for reducing the frequency of seizures in adults diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to antiepileptic medications."

The data presented in this summary also incorporate information provided by Medtronic in a 90-Day Update received on September 14, 2009 (pursuant to 21 CFR 814.20[e]). Please note that this update did revise the reporting of a small number of Blinded Phase adverse events; these revisions had minimal impact on the overall safety and effectiveness data for the Blinded Phase that were presented in the supplement as it was originally submitted to FDA.

2. Device Description

The Medtronic DBS System for Epilepsy uses an implantable neurostimulator to deliver electrical stimulation, bilaterally, to the anterior nucleus of the thalamus (AN-T) in the brain. The "system" that provides this therapy includes the implanted components (a neurostimulator, two leads, and two extensions that connect the leads to the neurostimulator) and external accessories. The external accessories are used during the implantation procedure or for programming the neurostimulator. All components of the device with the exception of the Intercept Patient Programmer are currently approved for other DBS indications.

Although the clinical data were collected with the Deep Brain Stimulation Kinetra Neurostimulation System (henceforth, to be referred to as the "Kinetra System" or simply "Kinetra"), the sponsor requests approval for the Deep Brain Stimulation Activa PC System for Epilepsy (henceforth, to be referred as the "Activa PC System" or simply "Activa PC"). Both the Kinetra and Activa PC Systems are approved for the treatment of essential tremor and Parkinson's Disease (Kinetra via P960009/S027, approved on December 16, 2003; Activa PC via P960009/S052, approved on April 7, 2009).

Compared to the Kinetra implantable pulse generator (IPG), the main differences of the Activa PC IPG include a smaller can size, the ability to stimulate using constant current in addition to constant voltage, and additional programmability options. The basic functionality and stimulation limitations, however, are the same for both systems. Table 1 summarizes Kinetra's programmability compared to that of the Activa PC. Due to the decrease in size, the Activa PC battery is also smaller, which does impact the expected battery life with equivalent programming (2.7-5 years for the Activa PC versus 3-6.6 years for Kinetra with dual program use).

The Activa PC can be used with Medtronic's two PMA-approved DBS leads: models 3387 and 3389. Each has four 1.5 mm-long platinum/iridium electrodes near the tip of each lead that

deliver stimulation to the target site. Model 3387 (which was used exclusively in the clinical study) has electrode spacing of 1.5 mm edge-to-edge, while this spacing is only 0.5 mm for Model 3389. To justify the use of the 3389 lead in addition to the 3387, Medtronic states that the variations in the size of the ANT observed during the trial are such that neurosurgeons may want a lead that has smaller electrode spacings to enable stimulation of more of the ANT, or different parts of the ANT. Other than the spacing of the electrodes, the 3387 and 3389 leads are identical.

The Activa PC System, like the Kinetra System, includes an external test stimulator (ENS) for intraoperative use. In the clinical study, the Kinetra ETS was not used. Functionally, the Activa PC ENS is similar to the implanted neurostimulator. However, since external trial stimulation was not used in the clinical trial, its clinical utility has not been established.

There is also a difference between the Access Therapy Controller (the Kinetra's patient programmer) and the Intercept Patient Programmer (for Activa PC). Whereas the Access Therapy Controller has no display and relies instead on color-coded lights and telemetry beeps to indicate device status and confirm user actions, the Intercept Patient Programmer has a LCD display that provides visual information for the patient. Furthermore, in the study, subjects were instructed to "activate" stimulation at the onset of a seizure. The term "activation" meant restarting the stimulation cycle (one minute on, five minutes off in the Blinded Phase); this was accomplished by using the Access Therapy Controller to turn the stimulator off, and then on again. The Intercept Patient Programmer was designed to incorporate a dedicated "seizure" button to initiate the stimulation cycle (i.e., it is now accomplished with a single button-press).

Based on our review of the two systems, FDA has concluded that the Activa PC would offer therapy that is comparable to what was provided by the Kinetra during the study.

3. Proposed Indications for Use

The sponsor proposes the following Indications for Use: "Bilateral anterior thalamic nucleus stimulation using the Medtronic DBS System for Epilepsy is indicated as adjunctive therapy for reducing the frequency of seizures in adults diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to antiepileptic medications."

The Panel will be asked to consider the proposed indications for use and discuss whether they are supported by the data in the PMA.

4. Regulatory History

The clinical study of the Kinetra Neurostimulation System for Epilepsy was conducted under IDE G030065. As of the writing of this Summary, the IDE remains open, but enrollment is closed. All subjects still active in the study continue to be followed.

The PMA panel-track supplement P960009/S068 was received by FDA on June 9, 2009, and was filed on June 24, 2009. A 90-Day Update to the PMA supplement was received by FDA on September 14, 2009.

5. Pre-Clinical Studies

The clinical study was conducted utilizing the Kinetra System. This system was under review as a PMA supplement (P960009/S027) for the Essential Tremor and Parkinson's Disease indication at the time the original IDE application was submitted. The data from the pre-clinical studies that were included with the PMA supplement were applicable to the IDE, and additional pre-clinical testing was not required for the IDE.

With the exception of the Intercept Model 37441 Patient Programmer, all components of the proposed DBS System for Epilepsy are commercially approved as part of the Medtronic Activa PC Neurostimulation System for Tremor Control and Parkinson's Disease (P960009/S052). Therefore, the preclinical tests of these components have not been repeated for the supplement under review.

The Intercept Model 37441 Patient Programmer is a derivative of the patient programmer developed for use with the Activa PC Neurostimulation System for Tremor Control. Modifications were made to adapt the programmer for use by epilepsy patients. These included the incorporation of a seizure button (as discussed above in the device description), soft key control of neurostimulator on/off activations and simplified navigation. To verify and validate these changes, software testing, system validation and human factors validation were completed to FDA's satisfaction.

The Medtronic DBS systems have specific MRI conditional labeling based on testing results. As noted in Section 6.1, subjects who had failed vagus nerve stimulation (VNS) therapy were candidates for the study, provided the VNS IPG was removed either before or at the time the DBS system was implanted. Because of the helical design of the VNS electrode, VNS leads cannot easily be removed from the nerve, and are generally left in place (i.e., the subjects have abandoned leads). According to Cyberonics's guidelines, no more than 4 cm of the lead body should be left attached to the electrode. Medtronic has not provided testing to establish guidelines for the use of MRI when both their DBS system and abandoned VNS leads are present.

Considering that 49 of the 110 implanted subjects had abandoned VNS leads, the Panel will be asked whether testing should be conducted prior to approval, or if a warning in the labeling about the lack of testing would be sufficient to assure patient safety.

6. Clinical Study Investigational Plan

To support the safety and effectiveness of its neurostimulation system for epilepsy, the sponsor has provided the results of a randomized, prospective multi-center clinical trial, titled "Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy", or SANTÉ.

Following is a summary of the SANTÉ study's eligibility criteria, efficacy and safety objectives, the measures used to evaluate the objectives, the sample size, and the study phases.

6.1. Eligibility Criteria

In reviewing the following eligibility criteria, please note that the study allowed for the inclusion of subjects that underwent one (and sometimes more) previous non-drug

treatments. In particular, subjects were not immediately excluded if they had been previously been implanted with a VNS system for epilepsy.

6.1.1. Inclusion criteria

To participate in the study, the subjects are required to meet all of the following criteria:

- Partial-onset seizures with or without secondary generalization. The final determination is made by the investigator based on a clinical description of the seizures and previous diagnostic testing that includes, at a minimum, video/clinical electroencephalogram (EEG) that captures at least 1 ictal event
- Anticipated average of 6 or more partial-onset seizures (with or without secondary generalized seizures) per month during the Baseline Phase, with no more than 30 days between seizures during the Baseline Phase
- Refractory to antiepileptic drugs (AEDs). Subjects are considered refractory if they failed at least 3 AEDs due to lack of efficacy.
- Receiving 1 to 4 currently marketed AEDs
- Be between 18 and 65 years of age, inclusive, at the time of lead implant
- If female, have a negative serum pregnancy test at the Baseline week -12 visit and, if sexually active, using a reliable form of birth control, surgically sterile, or at least 2 years postmenopausal
- Willing and available to complete the diary with or without the assistance of a caregiver
- Ability of the subject or legal representative to understand and provide signed consent for participating in the study
- Willing and available to attend visits as scheduled and to comply with the study protocol

6.1.2. Exclusion criteria

Subjects were excluded from study participation if they met any of the following criteria:

- Multilobar (>3 different lobes) anatomic areas of seizure onset
- Symptomatic generalized epilepsy
- AED(s) discontinued or started within the 30 days prior to the Baseline week -12 visit or any AED changes (to, e.g., total daily dose or formulation) within 14 days prior to the Baseline week -12 visit. Subjects on phenobarbital, primidone, or zonisamide were excluded if there were any changes within 30 days prior to the Baseline week -12 visit.
- Use of 3 or more doses of rescue medications (e.g., acute benzodiazepines) within a single 48-hour period in the 3-month period prior to the Baseline week -12 visit
- Averaged more than 10 complex partial seizures/day over the 3-month period prior to the Baseline week -12 visit
- Experiences only simple partial seizures that have no outward clinical manifestations observable by either the subject or caregiver
- Any episode of convulsive status epilepticus within the 12 months prior to the Baseline week -12 visit

- Previous diagnosis of psychogenic/nonepileptic seizures
- Surgical candidate for, and willing to undergo, partial temporal lobectomy or lesionectomy
- Within the 5 years prior to the Baseline week -12 visit, had a magnetic resonance image (MRI) showing evidence of a neurological condition that was likely to progress (e.g., brain tumor, active encephalitis, active meningitis or abscess, arteriovenous malformations or cavernous angiomas that were likely to progress)
- Diagnosed with a progressive or degenerative neurological disorder affecting the brain
- IQ less than 70 based on the Baseline week –12 WASI (Weschler Abbreviated Scale of Intelligence) test
- Significant medical condition that could worsen during the study period
- Presence of any of the following within 5 years prior to the Baseline week -12 visit: psychiatric illness hospitalization, suicide attempt or symptoms of psychosis (hallucinations, delusions) unrelated to an ictal state, a postictal state or a medication
- Malignancy or history of malignancy within 5 years prior to the Baseline week -12 visit (excluding resected basal cell carcinomas)
- Presence of implanted electrical stimulation medical device anywhere in the body (e.g., cardiac pacemakers, spinal cord stimulator) or any metallic implants in the head (e.g., aneurysm clip, cochlear implant). Vagus nerve stimulators are allowed if the device has been turned off for at least 30 days prior to the Baseline week -12 visit and the subject agrees to have the generator explanted prior to or at the time of the Kinetra Neurostimulator implant.
- Risk factors that would put the subject at risk for intraoperative or postoperative bleeding. This includes administration of any antiplatelet or anticoagulant medication in the 7 days prior to surgery, chronic anticoagulant use, or chronic aspirin use of greater than 325 mg/day, and any subject with a history of hemorrhagic stroke.
- History of substance abuse within the last 5 years
- Condition or disease that is known to require repeat MRIs
- Enrolled in another investigational device, drug, or surgery study or has completed the required follow-up phase in an investigational device, drug, or surgery study less than 30 days prior to the Baseline week -12 visit

6.1.3. Implant Criteria

If the implant criteria were not met, the subject was either terminated from the study or the subject repeated the Baseline Phase (one time allowed only). Subjects who repeated the Baseline Phase needed to meet the inclusion, exclusion, and implant criteria again.

6.1.3.1. Implant Inclusion Criteria

In order to continue to implant, the subjects had to have met the following inclusion criteria during the Baseline Phase:

- Experienced an average of 6 or more partial-onset seizures (with or without secondary generalized seizures) per month, with no more than 30 days between seizures
- Remained on the same AEDs, at the same total daily dose(s)
- Completed at least 70 days of diary information
- Attended scheduled visits
- Platelet count, prothrombin time (PT), and international normalization ration (INR) within normal limits (per center's reference range) as measured at the Baseline week 0 visit (or upon retest)
- If female, had a negative serum pregnancy test at the Baseline week 0 visit and if sexually active continued using a reliable form of birth control, was surgically sterile, or was at least 2 years postmenopausal
- Not on valproic acid/valproate or, if on valproic acid/valproate, bleeding time within normal limits (per the reference range used at the center) at the Baseline week 0 visit (or upon retest) (If the laboratory at the center did not perform bleeding time, a platelet function assay could be used.)

6.1.3.2. Implant Exclusion Criteria

In order to continue to implant, the subjects had to not have met any of the following exclusion criteria during the Baseline Phase:

- Use of 3 or more doses of rescue medications (e.g., acute benzodiazepines) within a single 48-hour period
- Averaged more than 10 complex partial seizures/day
- Any episode of convulsive status epilepticus
- Risk factors that would put the subject at risk for intraoperative or postoperative bleeding. This included administration of any antiplatelet or anticoagulant medication in the 7 days prior to surgery, chronic anticoagulant use, or chronic aspirin use of greater than 325 mg/day, and any subject with a history of hemorrhagic stroke.

6.2. Study Objectives and Outcome Measures

6.2.1. Primary Efficacy Objective

The stated primary efficacy objective was to "demonstrate that the reduction in the seizure rate in the active group is greater than in the control group."

This objective was evaluated using the total number of seizures (regardless of type) experienced by each subject; this was recorded using a diary.

6.2.2. Secondary Efficacy Objectives

The stated secondary objectives were as follows:

- To demonstrate that the proportion of responders (i.e., subjects who experienced at least a 50% reduction in seizures when compared to the baseline phase) in the active group is greater than in the control group.

- To demonstrate that the mean percentage of seizure-free days and maximum length of seizure-free intervals in the active group is greater than in the control group.

- To demonstrate that the proportion of treatment failures in the active group is less than in the control group. A treatment failure was defined as a subject who 1) required 3 or more doses of rescue medication within 48 hours, 3 times during the Blinded Phase, or 2) had 3 episodes of convulsive status epilepticus during the Blinded Phase.

Characterization as a responder was determined based on the seizure counts recorded in the subject diaries.

6.2.3. Safety Objectives

The two stated safety objectives were as follows:

- To characterize the adverse events experienced with the deep brain stimulation (DBS) system stimulating the anterior nucleus in subjects with refractory epilepsy.

- To characterize the incidence of sudden unexplained death in epilepsy (SUDEP) with the DBS system stimulating the anterior nucleus in subjects with refractory epilepsy.

Evaluation of these objectives was based on the adverse events experienced by subjects during the study. The investigator reported each adverse event in one of the following classifications:

- Surgery/anesthesia
- Programming/stimulation
- Lead
- Extension
- Lead/extension tract
- Neurostimulator
- Neurostimulator pocket
- Burr hole site

- Subject
    - New illness, injury, or condition
    - Pre-existing medical condition (further subdivided into
        - usual range of symptoms for this subject, or
        - worsening or exacerbation)
- Drug
    - Drug side effects/toxicity
    - Allergic reactions/sensitivity to drug
    - Other, specify

Serious adverse events (SAEs) were defined as an adverse event that meets one of the following criteria:

- Results in inpatient hospitalization
- Results in prolonged existing hospitalization
- Is life threatening (i.e., the subject was at risk of death at the time of the event)
- Results in subject death
- Results in persistent or significant disability/incapacity
- Results in permanent impairment of a body function or permanent damage to a body structure
- Necessitated medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

6.2.4. Additional Study Measures

The purpose of the additional study measures was to characterize certain types of information in the study population for exploratory purposes.

- To characterize seizure type and severity experienced during the Baseline and Blinded Phases in the active and control groups. Upon enrollment, study subjects were asked to classify their seizures according to International League Against Epilepsy (ILEA) classification (Figure 1). Since subjects could experience multiple kinds of seizures within a single class (e.g., two kinds of simple partial seizures), each type of seizure was assigned an unrelated letter (A, B, C, etc.).

- To characterize the number of Access Therapy Controller activations during the Blinded Phase in the active and control groups. The Access Therapy Controller allowed the subject to initiate a stimulation cycle to abort a seizure. This information was recorded automatically by the patient controller.

- To characterize the scores of the Quality of Life in Epilepsy (QOLIE-31), the subject satisfaction, and subject outcome questions in the active and control groups.

- To characterize the results of the neuropsychological testing in the active and control groups. This is described further in later sections of this summary.

- To characterize health care resource utilization in the active and control groups, as defined by the type of utilization (e.g., hospitalization, urgent care, etc.).

- To characterize the number of times subjects in the active and control groups used rescue medications. This was recorded as the number of subjects who required rescue medications, and the mean number of uses.

6.3. Study Design

6.3.1. Statistical Methodology

The primary efficacy analysis utilized a generalized estimating equation (GEE) model to test for a difference between seizure rates in the active and control groups in the Blinded Phase. The response variable in the GEE analysis was the seizure count (not the percent change or the change). The log of baseline count was used in the model as a covariate to account for the differences of subjects at baseline.

The remainder of the analyses utilized chi-square tests for categorical responses, Wilcoxon rank-sum or Wilcoxon signed-rank tests for non-normally distributed continuous endpoints, and t-tests or paired t-tests for normally distributed continuous endpoints.

Additional details regarding the methodology used to evaluate the data (mainly for the primary endpoint) can be found in Section 8.2.1.

6.3.2. Sample Size

The sample size for the SANTÉ was based on an expected 25% reduction in seizures for the active group vs. the control group. Subjects were randomized 1:1 to active or sham stimulation. The sponsor ultimately enrolled 157 subjects; of these, 110 were implanted, but only 109 were randomized. One subject exited the Blinded Phase prematurely due to an infection. This subject is discussed in detail in Section 8.1.5.

6.3.3. Phases

The overall study design schema is shown in Figure 2; each phase is described briefly here. Examination schedules for the Baseline, Operative, and Blinded Phases can be found in Table 2. The schedule for the Unblinded Phase appears in Table 3, and Table 4 contains the information for the Long-term Follow-up Phase.

6.3.3.1. Baseline Phase

Subjects who met the eligibility criteria and signed an informed consent entered a 3-month baseline phase prior to device implant.

During this phase, subjects' antiepileptic medications were held constant; subjects were also required to complete daily seizure diaries. For each day of the diary, a subject would note the type of seizure(s) experienced, and the number of each.

6.3.3.2. Operative Phase

At the conclusion of the baseline phase, subjects who met the study and implant eligibility criteria received the implanted system. Immediately following this was the 4-week Operative Phase, during which no subject received stimulation. Randomization to either the active or sham group occurred at the end of this period, and stimulation was turned on; the specific settings can be found in the first row of Table 5.

6.3.3.3. Blinded Phase

Following randomization and the initiation of stimulation, subjects entered the 3-month Blinded Phase. Stimulation settings were not allowed to be modified nor could medications be changed unless the subject experienced adverse events.

The primary and secondary effectiveness objectives are based only on the data that were collected during this 3-month period.

6.3.3.4. Unblinded Phase

At the 4-month post-implant visit, all subjects entered the 9-month Unblinded Phase. From this point forward, all subjects received active stimulation. During the Unblinded Phase, subjects could remain on the settings that were used in the Blinded Phase, or the settings could be modified to one of two group settings (see Table 5). Medications, however, were not changed unless deemed necessary due to an adverse event.

6.3.3.5. Long-Term Follow-Up Phase

At month 13, the subjects entered the Long-term Follow-up Phase, during which there were no limits on stimulation and AED adjustments. Subjects continued to maintain seizure diaries and to report adverse events. The programming options available during the Long-term Follow-up Phase of the study are also outlined in Table 5 (subject only to the limitations of the device and physician discretion).

7. Subject Accountability

The SANTÉ study has 157 subjects enrolled at 17 sites in the United States – the first implantation took place on March 22, 2004, and the last implantation occurred on June 27, 2007. A total of 109 subjects were randomized in the Blinded Phase, though 110 were implanted. Clinical data presented here are from the first enrollment date of December 11, 2003 through June 2, 2009 (cutoff date for the 90-Day Update submitted on September 14, 2009).

The flow chart in Figure 3 presents the accountability data graphically; this includes three additional discontinuations during the Long-term Follow-up Phase that were reported in the 90-Day Update.

Prior to implant, 47 subjects discontinued from the study for the following reasons: eligibility or implant criteria not met (24), subject changed his or her mind about participation (17), investigator decision due to safety reason (2), adverse event (1), death (1), lost to follow-up (1), and instability after VNS turned off (1).

No subjects discontinued from the study during the Blinded Phase. Five subjects discontinued from the study in the Unblinded Phase—one subject died and four discontinued due to an adverse event (implant site infection [2], neurostimulator pocket discomfort and involuntary muscle contractions). Fourteen subjects discontinued from the study in the Long-term Follow-up Phase—three subjects died, five discontinued due to an adverse event (implant site infection (2), psychotic disorder, meningitis, and cognitive disorder), one withdrew consent and five discontinued due to unsatisfactory efficacy.

Of the 110 implanted subjects, nine (8.2%) discontinued prematurely due to a nonfatal adverse event, as shown in Table 6. The adverse event most frequently leading to discontinuation was implant site infection (4 / 110, 3.6%). Implant site infections are discussed further in Section 12.3.2 of the PMA and Section 8.1.5 of this Summary. All subjects were in either the Unblinded Phase (n=4) or the Long-term Followup Phase (n=5) at the time of discontinuation. All subjects were receiving stimulation at the onset of the event that led to discontinuation.

More information about these discontinuations is presented in Section 8.1. In addition, Table 7 lists more specific reasons for all of the discontinuations.

7.1. Demographics and Baseline Characteristics

Demographics and baseline characteristics are provided in Table 8 and Table 9. Table 8 includes all 110 implanted subjects, while Table 9 is based on the Intent-to-Treat population, which includes 109 subjects. Neither table includes demographic information on the non-implanted subjects that discontinued during the Baseline Phase of the study.

Study subjects typically experienced more than one type of seizure. As noted in Table 10, complex partial seizures were the most common. The temporal lobe was the most common location of seizure onset (see Table 11).

7.2. Implantation Data

After completing a 12-week Baseline Phase, eligible subjects were implanted with a DBS system (implant information is described in Table 12). Deep brain stimulation leads were implanted bilaterally in the AN-T and connected subcutaneously to a neurostimulator via extensions. Surgery was done within 14 days of the week 0 visit.

For the 110 implanted subjects, the implantation procedure (defined as “skin to skin”) lasted a mean of 4.0 hours (SD=1.5 hours) with a median of 3.6 hours. The shortest surgery lasted 1.8 hours, and the longest lasted 8.2 hours.

Of the 49 subjects who had previously been implanted with a VNS system, 46 subjects had systems (generator and lead) in place at the time of enrollment into the SANTÉ study. All 46 subjects had the VNS device turned off for at least 30 days prior to the Baseline week -12

visit and had the generator explanted either before or at the time of DBS implant. For 43 of the 46 subjects, VNS leads were capped off or insulated. For two subjects, the VNS lead was transected at the carotid sheath, leaving nothing to cap. For the remaining one subject, Medtronic has been unable to confirm status of the VNS lead as the operative report is inconclusive and the surgeon is no longer at the institution.

7.3. Protocol Deviations

A total of 1166 deviations were reported during the study: 261 (Baseline through Unblinded Phases), 42 (Long-term Follow-up Phase), and 863 (visit window/data collection for Baseline through Long-term Follow-up Phases). Even though some subjects missed visits or had visits that were out of window, they continued to record seizures, adverse events, medication usage, and health care utilization. These were reported on a case report form at their next visit.

Table 13 summarizes the protocol deviations that occurred during the Blinded Phase. Only data from one subject were excluded from the primary analysis, but the data from this subject were included in the ITT analysis. The primary analysis included subjects who had recorded at least 70 days of seizure diary data during the Blinded Phase. The month 4 visit for the excluded subject was done early, which resulted in 66 days (rather than the required 70 days) between randomization and the month 4 visit (Blinded Phase). Therefore, this subject's data were excluded from the Primary Analysis.

From baseline through month 13, there were 63 deviations associated with epilepsy medications. Ten subjects had permanent AED changes during the baseline and Blinded Phase which excluded them from the per protocol analysis. Two of these subjects' deviations were related to implant criteria requiring stable medication in baseline.

8. Clinical Study Results and Analyses

8.1. Safety Results and Analyses

As stated previously, the SANTÉ study had the following safety objectives:

- To characterize the incidence of sudden unexplained death in epilepsy (SUDEP) with the DBS system stimulating the anterior nucleus in subjects with refractory epilepsy.
- To characterize the adverse events experienced with the deep brain stimulation (DBS) system stimulating the anterior nucleus in subjects with refractory epilepsy.

The datasets that were used for these objectives are described in Table 14. Please note that the FDA summary does not differentiate events based on the basis of their device relationship, since the relationship between the device and the adverse event in many cases is not clear cut.

For the first year after device implant (the Operative Phase through the Unblinded Phase), 808 adverse events were reported in 109 subjects. Serious adverse events (SAEs) were experienced by 40 subjects (36.4%) from the operative through the Unblinded Phase. Many of the adverse events can be reversed by adjusting the stimulation settings.

Common adverse events that occurred from the operative through the Unblinded Phase were paresthesia (19.1% of subjects), implant site pain (11.8%), implant site infection (9.1%), and lead(s) not within target (8.2%). Blinded Phase paresthesia events are outlined in Table 15; none of these events were serious. All leads not within the target required replacement. The infections led to device explant in five subjects (4.5%).

At month 13, the subjects entered the Long-term Follow-up Phase, during which there were no limits on stimulation and AED adjustments. Table 16 includes subjects with a greater than 50% worsening in seizure frequency at two years.

Table 17 lists all adverse events experienced, by organ system, from the Operative through Unblinded Phases of the study. Table 18 lists the adverse events that have been experienced during the Long-term Follow-up Phase.

The sections described below highlight important types of adverse events that were seen in the study and that should be considered in the discussion of the risk profile of the device.

The Panel will be asked to comment on the overall safety profile of the device in the proposed population.

8.1.1. Deaths and SUDEP

Six subject deaths were reported (inclusive of all study phases, Baseline through Long-term Follow-up; see Table 19). Determination of SUDEP was made by the investigator and reviewed by the Data Safety Monitoring Board, utilizing accepted criteria. SUDEP is an anticipated SAE in this population. Criteria for determining whether a death may be SUDEP include the following:

- The subject must have suffered from epilepsy, defined as recurrent unprovoked seizures.
- The subject died unexpectedly while in a reasonable state of health.
- The death occurred suddenly (within minutes), when known.
- The death occurred during normal activities (e.g., in or around bed, at home, at work) and circumstances must have been seen as benign.
- An obvious medical cause of death was not found.
- The death was not the direct result of a seizure or status epilepticus.

Deaths were evaluated to determine if they met the SUDEP criteria and were classified as definite, probable, possible, unlikely, or not SUDEP. Rates of definite/probable and definite/probable/possible SUDEP per 1,000 person-years were calculated for implanted subjects (Table 20).

- Definite SUDEP must meet all of the above criteria and have sufficient descriptions of the circumstances of the death. In addition, a postmortem must have been performed.

- Probable SUDEP would fit all of the categories above except that postmortem results would not be available.

- Possible SUDEP would be reserved for cases where SUDEP cannot be ruled out but there is insufficient evidence about the circumstances of the death and no postmortem report is available.

- Unlikely SUDEP includes covariate where the circumstances make SUDEP highly improbable.

- The not SUDEP category includes deaths where other causes are clearly established.

The SUDEP rate was determined based on the SANTÉ study experience and on five previous pilot studies of DBS using the Medtronic device for the treatment of subjects with partial onset seizures. Three of the five centers participated in the Stimulation for Epilepsy Long-term Follow-up study. The other two centers did not participate in this long-term study, but agreed to provide information on the duration of stimulation and mortality status. The sponsor based their SUDEP rate calculation on the number of subjects that met the criteria for definite and probable SUDEP. FDA's SUDEP rate calculation (Table 20) is based on the number of subjects who died while receiving stimulation and who met the criteria for definite, probable or possible SUDEP.

The definite/probable/possible SUDEP rate for the study is 7.6 deaths per 1000 person-years (i.e., three deaths in 397 person-years of stimulation). At this time, the cause of the additional death reported in January 2010 is pending. At a 1997 panel meeting for a neurostimulation device indicated for a similar population, panel members thought that it was appropriate to compare the SUDEP rate in that study to a literature reported rate of 9.3 deaths per 1000 person-years for surgical candidates. (Dasheiff RM. Sudden unexpected death in epilepsy: a series from an epilepsy surgery program and speculation on the relationship to sudden cardiac death. J Clin Neurophysiol. 1991;8:216-222.)

The Panel will be asked whether the observed SUDEP rate is acceptable for the indicated population.

8.1.2. Suicidality events

There were ten events related to the Medical Dictionary for Regulatory Activities (MedDRA) terms of completed suicide, suicide attempt, depression suicidal, suicidal ideation, and intentional self injury; these are outlined in Table 21. Two events occurred in subjects who discontinued during the Baseline Phase, one event occurred in the Blinded Phase, one in the Unblinded Phase, and six in the Long-term Follow-up Phase. In other words, eight events occurred in implanted subjects (8 / 110, 7.3%). Five of the eight events were categorized as serious. Six of the eight subjects (6 / 8) had a medical history of depression or suicidality at the start of the study. At the time of event onset, the subjects had received stimulation for an average of 730 days (range: 94 to 1353 days).

All of the subjects were taking at least one of the antiepileptic medications that were included in a January 2008 FDA alert about the potential for increased suicidality associated with the use of epilepsy medications (this resulted in a warning for all epilepsy medications to that effect). Two of the eight events (2 / 8) were mild, one of which resolved. Two events (2 / 8) were moderate, both of which resolved. Four events (4 / 8) were severe: two resolved, one is ongoing, and one resulted in death. The subject that died (completed suicide) was not receiving active stimulation at the time of the event; the neurostimulator battery was depleted and the subject was being scheduled for a replacement procedure at the time of the event.

Because of these events, the sponsor has agreed to add the following warning: "Depression monitoring – During treatment, patients should be monitored closely for new or changing symptoms of depression."

In light of depression and suicidality events that occurred throughout the entire duration of the trial, the Panel will be asked whether they believe the device provides a reasonable assurance of safety. Additionally, the Panel will be asked to provide labeling recommendations to mitigate risk of suicidality with use of the device.

8.1.3. Intracranial hemorrhage

Five asymptomatic intracranial hemorrhage events were reported; all were discovered on post-procedural imaging.

Intracranial hemorrhages were radiologically detected after the initial implant procedure in four of the five subjects (3.6%, 4 / 110). In one of the five cases, imaging (CT scan) was done after a fall sustained during a seizure after removal of the entire system. The imaging in this case revealed an intraventricular hemorrhage that did not correlate with the lead tracts.

Table 22 includes events coded to four different MedDRA preferred terms: hemorrhage intracranial, intraventricular hemorrhage, subdural hematoma, and post procedural hemorrhage.

8.1.4. Status Epilepticus

Status epilepticus occurred in five subjects (5/110, 4.5%), as presented in Table 23. Four of the five events were nonconvulsive in nature. Four of the five subjects required hospitalization for the event; narratives for these four SAEs are found in Section 14.3.3.1 of the PMA (Volume 5). The status epilepticus event in one subject did not meet any of the criteria for a serious adverse event (as outlined in Section 6.2.3); the event occurred the day of the initial implant procedure and the subject was already hospitalized and duration of stay was not prolonged.

Two of the subjects were receiving stimulation at the time of the event, while three of the five events occurred in subjects who were not receiving stimulation.

8.1.5. Infection

Inclusive of the operative through Long-term Follow-up Phase, 14 subjects experienced an implant site infection; 10 of these subjects experienced the event within the first year after implant.

One subject (not randomized) developed an infection after implantation, and the device was explanted. After the infection resolved, the subject underwent re-implantation. Rather than be randomized, the subject skipped the Blinded and Unblinded Phases, since a sufficient number of subjects had been randomized.

Another subject randomized to the control group developed an infection which required device explant. After the infection resolved, the subject underwent re-implantation. Rather than be re-randomized, the subject entered the Long-term Follow-up Phase, since a sufficient number of subjects had already been randomized.

Six subjects had a complete system explant due to infection, four without replacement and two with subsequent replacement. In addition, two neurostimulators with four extensions were removed (in two subjects) due to infection, and one subject was subsequently reimplanted. In many cases, the infection was confined to a single component; however, entire systems were removed to avoid spread of the infection among the device components.

8.1.6. Seizure Adverse Events Associated with Stimulation Initiation

As noted previously, all active subjects were assigned the same stimulation settings during the Blinded Phase, except in the case of adverse events. When stimulation was initially turned on, three subjects in the active group experienced increased, worsening, or new seizures during the first week of stimulation.

Active subjects (first week of the 3-month Blinded Phase, i.e., after the week 4 visit)

- One subject experienced a new simple partial seizure starting five days after being randomized to the active group at week 4. There was no intervention and the event is ongoing. (The subject has experienced only four other seizures of this type through month 33 of the study.)
- "Subject A" had 210 complex partial seizures in the three days after turning on his stimulator starting the day of randomization. This new type of complex partial seizure resolved with reprogramming and the subject has not had another seizure of that type (see Section 8.2.2.1 for information about this subject as it pertains to the effectiveness analysis; additional safety information on this subject is provided below).
- One subject had a longer and more intense aura as part of the subject's simple partial seizure starting the day of the week 4 visit. Stimulation was reprogrammed at the week 6 visit and the event resolved by month 2.

Two subjects that were assigned to the control group also experienced seizure-related adverse events once their stimulation commenced at the start of the Unblinded Phase.

Prior Control subjects (first week of Unblinded Phase)

- One subject had a longer than normal simple partial seizure the day of the month 4 visit after stimulation was turned on. It resolved the same day with no intervention.
- One subject reported confusion that started the day of the month 4 visit after stimulation was turned on. The subject was hospitalized after an EEG showed status epilepticus. Voltage was decreased, and the event resolved within 6 days (see SAE narrative in Section 14.3.3.1 of the PMA for more information about this event).

During the Baseline Phase, "Subject A" experienced an average of 19 total seizures per month. On the first day of the Blinded Phase, the subject was randomized to the active group and stimulation was turned ON (5 volts, 90 μs, 145 Hz). After that, the subject had 70 seizures of a new type of complex partial seizure (designated as seizure type E). These new type E seizures were similar to a seizure type the subject already had (type A, also complex partial seizure), but with slightly different clinical manifestations and significantly shorter seizure duration. The new type E seizure was 10 seconds long with a 1-minute postictal period, and the type A seizure was 3½ minutes long with a 30-minute postictal period.

On the following day, "Subject A" had 100 more type E seizures and was instructed by the investigator to turn the device OFF using the hand-held Access Therapy Controller. Upon doing so, the type E seizures stopped. An office visit was scheduled for next day; prior to this visit, the physician instructed the subject to turn the device back ON. The new type E seizures resumed, resulting in the subject having an additional 40 seizures. During the office visit, stimulation was turned down to 4 volts. Upon doing so, the type E seizures stopped and did not recur. In total, the subject had 210 type E seizures in 3 days. Starting at month 7 and continuing through month 10, the subject was exposed to the previous stimulation parameters (5 volts, 90 μs, 145 Hz) with no recurrence of the type E seizures. In addition, the subject has received up to 9 volts of stimulation after month 13 with no recurrence of these type E seizures.

In light of instances of increased, worsening, or new seizures, the Panel will be asked whether they believe the device provides a reasonable assurance of safety, and to provide labeling recommendations.

8.1.7. Other Serious Adverse Events

Inclusive of all study phases (Baseline through Long-term Follow-up), 69 of the 157 enrolled subjects (43.9%) experienced 109 SAEs.

During the Blinded Phase, serious adverse events besides those described above are captured in Table 24. Serious adverse events over the course of the whole study, inclusive of all phases, are outlined in Table 25.

8.1.8. Adverse Events in the Blinded Phase

Events that occurred in greater than 5% of subjects during the Blinded Phase (in one or both treatment groups) are presented by treatment group in Table 26. Events are ordered by the difference between groups: a positive difference indicates the event was more frequent in the active (stimulation on) group and a negative difference indicates it was more frequent in the control group.

There was a higher frequency of depression and memory impairment events in the active group compared to the control group. Although not discussed at length below, there were more confusional state and anxiety events in the active group than in the control group, while there were more injury events in the control group than in the active group.

8.1.8.1. Subjects with Worsening Seizure Frequency in the Blinded Phase

As can be seen in Table 27 and Figure 4, a number of subjects had increased seizures over the course of the Blinded Phase (10 in the active group and 16 in the control group). Most prominent among these is "Subject A" (active group); this subject was noted previously in Section 8.1.6, and is discussed further in Section 8.2.2.1.

In light of the number of subjects experiencing a worsening seizure frequency in the Blinded Phase, the Panel will be asked whether they believe the device provides a reasonable assurance of safety, and to provide labeling recommendations as needed.

8.1.8.2. Depression Events in the Blinded Phase

During the Blinded Phase, spontaneously self-reported worsening or new onset depression occurred in 14.8% (8 / 54) of the active subjects and 1.8% (1 / 55) of the control subjects (Table 28). Two of these subjects (one in the active group and one in the control group) did not have a medical history of depression. No subject discontinued from the study due to depression alone.

Of the eight depression events in the active group subjects, one was serious (requiring hospitalization); of the seven non-serious events, four of the events resolved and three were ongoing. The ongoing depression events were mild in severity in one subject and moderate in severity in two subjects and were being treated with medication and/or counseling.

The one case of depression in the control subject was mild and ongoing, and this subject was being treated with medication and was referred to a psychiatrist.

While there was a higher incidence of spontaneously self-reported depression in the active vs. control group, no overall differences were observed between groups on the Profile of Mood States depression (POMS-D) scale from baseline to month 4 (Table 29). The observed changes in mean scores in both groups compared to baseline are considered clinically insignificant (mean change of less than one standard deviation). However, the mean scores are reflective of mild depression in both the active and control groups at baseline and at the end of the Blinded Phase.

Given the incidence of depression-related events in the Blinded Phase, the Panel will be asked whether they believe the device provides a reasonable assurance of safety, and to provide labeling recommendations. (see also Section 8.1.2)

8.1.8.3. Memory Impairment in the Blinded Phase

Spontaneously self-reported worsening or new onset memory impairment occurred in 13.0% (7/54) of the active subjects and 1.8% (1/55) of the control subjects (Table 30). Of the eight subjects with memory impairment, two had a previous history of memory impairment. All of these events resolved, and no subject discontinued from the study at any point due to memory impairment.

Of the seven in the active group, five of the events resolved without intervention and two resolved with reprogramming of the device. The one case of memory impairment in the control group resolved without intervention.

Considering the incidence of memory impairment events in the Blinded Phase, the Panel will be asked whether they believe the device provides a reasonable assurance of safety, and to provide labeling recommendations.

8.1.8.4. Neuropsychological Testing in the Blinded Phase

Results of the neuropsychological testing showed that the baseline scores for both the active and control groups indicated mild impairment in attention, memory, and expressive language and mild depression, tension/anxiety, mood disturbance and confusion. Neuropsychological test results (Table 31) showed no significant differences between the active and control groups during the Blinded Phase, as well as no detrimental effects (worsening from baseline) of the stimulation on the group as a whole in the Unblinded Phase of the study.

Eight control subjects were removed from the Blinded Phase analysis because the neuropsychological testing was conducted after the month 4 programming had been completed (i.e., stimulation was turned on before testing). One control subject did not have any testing conducted at the month 4 visit.

8.1.8.5. Rescue Medication in the Blinded Phase

Rescue medication use was allowed during the course of the study. Results show that 12 of the subjects in each group used a rescue medication at least one time during the Baseline Phase. During the Blinded Phase, 12 subjects in the active group and 12 in the control group used a rescue medication. Subjects in the active group had a mean ± standard deviation rescue medication use of 0.79 ± 1.83 while subjects in the control group had a mean medication use of 2.27 ± 7.59 over the 84 day period. Refer to Table 32 and Table 33.

8.1.8.6. Healthcare Utilization in the Blinded Phase

Healthcare utilization was assessed as an exploratory endpoint. Persons with epilepsy are at a higher risk for incurring accidental injury, such as contusions, wounds,

abrasions, fractures, and concussions. There were no significant differences between subjects in the active and control groups. However, there was a trend towards less healthcare utilization in the active group. Refer to Table 34.

8.1.9. Device Explants, Replacements, and Revisions

Modifications of the device consisted of explant, replacement, or revision of the device or one or more components of the device (see Table 35). A total of 12 subjects had the complete system explanted. The most common cause for the entire system to be modified was infection; six subjects had a complete system explanted due to infection, four without replacement and two with subsequent replacement. In addition, two neurostimulators with four extensions were removed (in two subjects) due to infection, and one subject was subsequently reimplanted. In many cases, the infection was confined to a single component; however, entire systems were removed to avoid spread of the infection among the device components.

The most common causes for neurostimulator modification were pain/discomfort/paraesthesia (in four subjects) and migration or movement in three subjects. Fourteen leads (in nine subjects) were replaced due to not being within the anterior nucleus which was the most common cause for lead modification. Lead extension modifications were most commonly due to fracture and migration/dislodgement. Nine extensions were replaced in four subjects due to fracture and four extensions were repositioned in three subjects due to migration/dislodgement.

Normal battery depletion accounted for 65 neurostimulator replacements in 43 subjects. A Kaplan-Meier survival analysis showed that half of the subjects in the study (i.e., median survival) needed a neurostimulator replacement after 36.8 months (3.1 years).

8.2. Study Results – Efficacy Analysis

The Baseline Phase consisted of three 28-day intervals and the Blinded Phase consisted of three 28-day intervals. The number of seizures was recorded for each 28-day interval and was used as the count data for the model.

The primary analysis included subjects who had recorded and documented at least 70 days of seizure frequency data in both the Baseline and Blinded Phases. Additional analyses were conducted in order to support the primary efficacy analysis.

The sensitivity analyses include the following:

- Intent-to-treat (ITT) analysis: Subjects who had a minimum of 1 diary day collected in the Blinded Phase and a minimum of 1 diary day collected in the Baseline Phase
- "Per protocol" analysis: subjects who did not have a physician-prescribed permanent change to AED medications or total daily dose of AED medication from baseline to the end of the Blinded Phase.
- "As treated" analysis: subjects who received their assigned treatment without interruption during the entire Blinded Phase.

The efficacy analyses (which are outlined in Table 36) take into account only the Blinded Phase of the study since the SANTE trial was not designed to evaluate the long-term effectiveness of the device.

8.2.1. Statistical Methodology

The primary hypothesis was that the active group will have a statistically significant reduction in the seizure rate as compared with the control group.

H_0: $\beta_1 \geq 0$

H_A: $\beta_1 < 0$

Where β_1 is the coefficient of the treatment effect term in the generalized estimating equations (GEE) model.

The following is the full GEE model with the mathematical form of:

$$\log(E(Y_{ij})) = \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \beta_3 x_{i1}x_{i2} + \beta_4 \log(\text{baseline seizure count}_i) + \log(t_{ij}) + \beta_{5-7} \log(\text{baseline covariates}_i)$$

where

j = 1, 2, 3 (visit index)
i = 1, …, n (subject index)
Y_{ij} = number of epileptic seizures in interval j
t_{ij} = length of interval j
x_{i1} = treatment (0: control group; 1: active group)
x_{i2} = visit (-1: visit 1, 0: visit 2, 1: visit 3)

The following bullets describe the preplanned specifications for the GEE analysis. It is also noted here if a test did not need to be conducted, and the reason for this result. SAS PROC GENMOD was used to conduct the GEE analysis using the following:

- A test for the Missing Completely at Random (MCAR) assumption. The plan allowed for a test of the Missing Completely at Random assumption. Since there were no visits entirely missed, there was no need to test this assumption.

- The probability distribution model (i.e., Poisson or Negative Binomial) was chosen using "Goodness of Fit" statistics to select the model with the best fit. The Negative Binomial distribution was selected.

- The number of seizures experienced during the Baseline Phase was included as a covariate and was calculated as the log of the total seizure counts adjusted for an 84-day baseline (three 28-day intervals).

- The log of the actual number of days with diary entries between each follow-up visit was included as an offset parameter.

- Correcting for over-dispersion. This was not needed as the Negative Binomial model was used which already corrects for over-dispersion without using an additional parameter.

- An exchangeable correlation structure was used.

- Additional prespecified baseline covariates were tested using stepwise procedures. The baseline covariates that were investigated were age, gender, and number of years with epilepsy prior to enrollment, and seizure onset location of epilepsy. The seizure onset locations were: frontal, temporal, parietal, occipital, diffuse or multifocal, and other. If the subject had more than one seizure onset location, the seizure onset location of the seizure type with the highest frequency was used in the analysis.

8.2.2. Primary Objective

As noted previously, the primary objective of the study was to demonstrate that the reduction in the seizure rate in the active group is greater than in the control group.

The prespecified primary endpoint (i.e., the GEE model) which included adjustments for baseline seizure frequency, log of age, time effect (visit), and visit-by-treatment interaction, failed to meet the prespecified primary endpoint, p=0.483 (see Table 37). The variables in the final model and their corresponding p-values are:

- Log of Baseline Seizures: $p < 0.0001$
- Treatment (Active vs. Control) $p = 0.48$
- Visit (Month 1, 2, 3) $p = 0.07$
- Visit * Treatment $p = 0.07$
- Log of Age $p = 0.05$

While the covariate 'log of age' attains statistical significance, no clinical reason has been put forth to suggest that age should affect the number of seizures. The interaction between age and treatment is discussed further in the Section 8.2.2.4.

Table 38 and Table 39 provide median changes in seizures per month (the former as percent change); median seizure data was used due to the large variability in seizure counts. Figure 4 shows the percent reduction in seizure frequency over the Blinded Phase for each subject (each line represents an individual subject). As can be seen, only one subject (in the control group) became seizure free during the Blinded Phase. A total of 26 subjects (10 active, 16 control) had an increase in seizures over the course of the Blinded Phase, as compared to baseline.

As seen in Table 39, the baseline median seizure frequency for the active group was 18.4 and for the control group was 20.2. Following implant, the median seizures per month reduced by 3.3 seizures in both groups (Operative Phase). Subjects in the active group had an additional median reduction of 1.9 seizures, whereas the control subjects had a slight increase of 0.4 seizures (Blinded Phase). In other words, the difference in seizure

frequency reduction between the two groups over the entire Blinded Phase was 2.3 seizures per month.

With regards to the blinding assessment outlined in Table 40, subject responses are missing for three subjects at the week 6 visit (one subject in the active group and two subjects in the control group) and two subjects in the control group at the month 4 visit. In both groups, more subjects guessed the correct treatment assignment than guessed incorrectly.

In light of the difference in seizure reduction between the active and control groups of 2.3 seizures per month at the end of the Blinded Phase, the Panel will be asked whether they believe the device provides a reasonable assurance of effectiveness. The Panel will be asked to also consider the 3.3 median reduction in seizure frequency that was seen in both groups during the Operative Phase (i.e., prior to the initiation of stimulation).

8.2.2.1. Alternative Analysis (To Exclude "Subject A", Active Group)

The sponsor identifies one subject ("Subject A", discussed above in Section 8.1.6) as an outlier. At the month 1-2 visit, this subject worsened by 1347.1% in total seizure frequency, as compared with baseline, and then improved over time. From months 2-3 the change from baseline was 4.2%, and from months 3-4 the change was -49.2%.

Prior to the submission of the PMA supplement, FDA allowed the sponsor to propose an alternative analysis in which the data from "Subject A" was removed. In the alternative analysis, the overall Blinded Phase p-value (which resulted in p=0.483 when all eligible subjects are included) reaches statistical significance (p=0.043 with "Subject A" excluded). However, this decision was made before the PMA was submitted and before FDA had reviewed the complete dataset. During review of the PMA, FDA identified 10 subjects in the active group and 16 in the control group who had increased seizure frequency during the Blinded Phase (Figure 4). The protocol did not prespecify a specific seizure increase that would be considered an outlier and thus be excluded from the analysis.

For those models where a treatment-by-visit interaction is not significant at $p < 0.1$ and the data from "Subject A" are removed (i.e., ITT, Per Protocol, As Treated [95%], and As Treated [80%]) the difference between the two treatment groups for the entire Blinded Phase reaches a p-value <0.05.

For this alternative analysis, the median seizure reduction in the active group over the entire Blinded Phase increases from -5.2 to -5.4. Subsequently, the difference in median seizure reduction between the two groups increases from 2.3 to 2.5.

Considering that the study failed to meet its primary endpoint, the Panel will be asked whether they believe that the use of the proposed alternative analysis demonstrates that the device provides a reasonable assurance of effectiveness.

8.2.2.2. Proposed Exclusion of "Subject B" (Control Group)

Based on communication with FDA (December 6, 2007), the sponsor added a sensitivity analysis that excluded the data from a control subject ("Subject B") that was possibly unreliable.

Based on two observations, the study center suggested that the diary data of "Subject B" was likely to be unreliable or biased. As with all of the other randomized subjects, the center was blinded to the treatment group assignment. First, there was a new diagnosis of psychogenic (or non-epileptic) seizures. The new diagnosis was made on the basis of direct observation, inpatient EEG monitoring, and a history of seizure fluctuations according to social dynamics. Second, there were two different caregivers who helped record seizures during the study: the subject's mother and the subject's girlfriend. The investigator indicated that the girlfriend recorded fewer nocturnal seizures than the mother, and the subject started having the new onset psychogenic seizures that only occurred in the presence of the mother. Based on this information, the center thought that the diary data from this subject were unreliable and recommended that those data be excluded.

As seen in Table 37, when the data from "Subject B" is removed, the primary and alternative analyses (when "Subject A" is removed) do not demonstrate statistically significant differences: p=0.557 and p=0.062, respectively.

The exclusion of "Subject B" does not affect the median seizure reduction of the control group over the entire Blinded Phase; it remains -2.9. Therefore, the difference in median seizure reduction between the two groups is still 2.3 for the primary analysis, and 2.5 for the alternative analysis that excludes "Subject A".

8.2.2.3. Analysis of Results by Month in the Blinded Phase

During the Blinded Phase, the active group showed a continuous reduction in their total seizure rates from the baseline visit through the Blinded Phase, while the control group showed a reduction at month 1-2 and 2-3 but not month 3-4 (see Table 39). At month 3-4, the active group showed a statistically significantly greater reduction in seizures (least-squares means) compared with the control group regardless of which analysis was used (i.e., primary or alternative). The median total seizure frequency percent change from baseline to the end of the Blinded Phase was -40.4% for the active group compared with -14.5% for the control group for both analyses.

The sponsor pre-specified looking at a visit by treatment interaction, and if that was significant, each month would be analyzed. The p-value for this interaction was less than the 0.10 value Medtronic used to justify looking at the interaction, but the value was not less than 0.05. Also, "All Blinded" is not cumulative; it is the per-month average over the whole Blinded Phase.

The result of the sensitivity analyses show a p-value <0.05 between the active and control groups at the Month 3-4 visit regardless of the inclusion of the data from "Subject A" (see Table 37). The generalized estimating equations (GEE) model,

which included adjustments for baseline seizure frequency, log of age, time effect (visit), and visit-by-treatment interaction, showed if all subjects meeting the primary objective criteria are included (n=108), there is a statistically significant treatment effect at the Month 3-4 visit ($p<0.002$). In the alternative analysis, in which the data from "Subject A" was removed, the p-value for the treatment effect for the GEE analysis at the Month 3-4 visit is $p<0.003$. The observed difference in median seizure reduction between the active and control groups during the last month of the Blinded Phase was 26%.

While the overall difference in median seizure reduction between the active and sham groups at the end of the Blinded Phase was 2.3 seizures, the results from Month 3-4 alone (as seen in Table 39) demonstrate a difference of 6.5 seizures.

As noted in Table 41, there are variations in seizure counts from month to month, and seizure counts in the control group decreased during the Baseline Phase.

Considering that the primary prespecified analysis was based on comparison of the median seizure change from a three month baseline to the three month randomized phase (due to month-to-month seizure variability), the Panel will be asked whether they believe the month 3-4 analysis provides a reasonable assurance of effectiveness.

8.2.2.4. Interactions

The interactions between baseline covariates and the treatment were not pre-specified to be included in the model. However, there were significant interactions, most notably between the log of age and treatment. To understand the effect of age on the number of seizures, one must look at the age-treatment interaction. Table 42 shows the percent decrease in seizures above and below the median age and above and below the 75th percentile or the upper quartile.

In that table we see that the active treatment effect is stable, but there is wide variability in the control group depending on age. No reason has been given to suggest why age should be a significant predictor of the success of this device.

Similarly, there was a significant interaction between study site and treatment, even though the sample sizes at each site were very small. This interaction is attributed to the large variability in the responses and not to the direction of the effect between treatment and control. Knowing that the sample sizes at each site would be very small, FDA encouraged the sponsor to pre-specify a plan for pooling smaller sites together. The sponsor agreed, and in this pre-specified analysis, there was not a significant site by treatment interaction.

8.2.3. Secondary Objectives

There were no statistically significant differences between the active and sham groups on any of the secondary efficacy endpoints. These secondary endpoints further

characterized the clinical significance of a change in total seizure reduction. As noted previously in this summary, the secondary objectives were as follows (with results):

- **To demonstrate that the proportion of responders in the active group is greater than in the control group.**

  Responder rates between the active and control groups were not different (see Table 43). FDA performed a post hoc analysis using various definitions of responders, (e.g., 10, 20, or 30 percent) in the active versus sham groups. None of the differences in these analyses were statistically significant.

- **To demonstrate that the mean percentage of seizure-free days and maximum length of seizure-free intervals in the active group is greater than in the control group.**

  There was no statistically significant difference in percent change in seizure-free days or percent change in maximum length of seizure-free intervals between the active and control groups over the entire Blinded Phase (p=0.105 and p=0.498, respectively; see Table 44 and Table 45).

- **To demonstrate that the proportion of treatment failures in the active group is less than in the control group. A treatment failure is a subject who 1) requires 3 or more doses of rescue medication within 48 hours, 3 times during the Blinded Phase, or 2) has 3 episodes of convulsive status epilepticus during the Blinded Phase.**

  There were no treatment failures in either group during the Blinded Phase of the study (Fisher's Exact p-value: 1.000).

8.2.4. Additional Study Measures

As discussed above, the sponsor did not meet their predefined primary effectiveness endpoint or any of their predefined secondary endpoints. Therefore, these additional analyses should be considered exploratory; they are included since they provide additional information regarding safety and effectiveness. Because these are exploratory, the p-values for the tables associated with these objectives have been omitted in the FDA summary.

- **To characterize seizure type and severity experienced during the Baseline and Blinded Phases in the active and control groups.**

  The sponsor states that there was a difference between the groups (active better than control) in the reduction of subjects' prospectively defined "most severe" seizures. However, FDA does not agree with this conclusion since there were six subjects who had seizures noted as severe in the Blinded Phase, but did not have them in the Baseline Phase.

Table 46 (and Figure 5) shows the types of seizures that were recorded in the Baseline, Operative, and Blinded Phases. The type of seizure that subjects classified as "most severe" was analyzed in two ways. The first analysis includes subjects that did not experience a "most severe" seizure in baseline but did experience a "most severe" seizure in the Blinded Phase, calculating the percent change as 100%. The second analysis does not include any subject that did not experience a "most severe" seizure at baseline.

From this analysis we see that the active group experienced a nearly statistically significantly greater reduction in the complex partial seizures when compared to the control group. As the complex partial seizure was often the most severe seizure, the reduction in the "most severe" seizure was also nearly statistically significant.

It is also important to note that there was no difference between groups in seizure severity as assessed by the Liverpool Seizure Severity Scale (see Table 47).

- **To characterize the number of Access Therapy Controller activations during the Blinded Phase in the active and control groups.**

  The controller allowed subjects to turn the neurostimulator OFF and ON, which would start a new stimulation cycle at the time the controller was used. Subjects were instructed to use the device at the onset of a seizure.

  As can be seen in Table 48, there was no difference between the active and control groups in controller use. The data are shown by percentage of subjects in a particular "activation category" (range of activations) in Figure 7. Note: no activations were recorded in the range of 400 to 700.

- **To characterize the scores of the Quality of Life in Epilepsy (QOLIE-31), the subject satisfaction and subject outcome questions in the active and control groups.**

  There was no change in quality of life during the Blinded Phase (see Table 49). Three subjects were not included in this analysis due to missing data (one from the active group, two from the control group). An additional active group subject refused to answer portions of the QOLIE-31

  Study subjects were also asked about their satisfaction with the therapy at pre-determined points. Four subjects from the control group were excluded for missing data on the satisfaction question at month 4. As seen in Table 50, 55.5% of the active subjects were either very or somewhat satisfied with the therapy compared to 69.2% of the subjects in the control group at the end of the Blinded Phase.

In addition, subjects were asked at pre-determined points whether they would 1) go through the process again to achieve the same result, and 2) whether they would recommend the therapy to a friend. Subjects were excluded for missing data on therapy recommendation question at month 4 (one from the active group, and two from the control group), As seen in Table 51, more subjects in the control group as compared to the active group would go through the therapy again for the same result and would recommend the therapy to a friend.

There were no changes in employment status, driving status, living arrangements, or primary caregiver during the Blinded Phase (see Table 52). One control subject was not included in this analysis due to missing data.

- **To characterize the results of the neuropsychological testing in the active and control groups.**

  This information was provided in the safety section 8.1.8.4. Neuropsychological test results showed no significant differences between the active and control groups during the Blinded Phase, as well as no detrimental effects (worsening from baseline) of the stimulation on the group as a whole in the Unblinded Phase of the study.

  Of note regarding the Blinded Phase data in Table 31: One active subject did not have an intelligence score and one active subject did not have a subjective cognitive function score. In addition, eight control subjects were removed from the Blinded Phase analysis because the neuropsychological testing was conducted after the month 4 programming had been completed (i.e., stimulation was turned on before testing). This exclusion was not prespecified. One control subject did not have any testing conducted at the month 4 visit and one control subject did not have a POMS-D test at the month 4 visit. An additional two control subjects did not have an intelligence score at the month 4 visit, and one control subject did not have an intelligence score at baseline.

- **To characterize health care resource utilization in the active and control groups.**

  This information was provided in the safety section 8.1.8.6.

- **To characterize the number of times subjects in the active and control groups used rescue medications.**

  This information was provided in the safety section 8.1.8.5. There was no difference between groups in the number of times a subject used rescue medication.

8.2.5. Post-hoc Analyses

8.2.5.1. Previous Epilepsy Surgery

As seen in Figure 8, improvements in the median total seizure frequency were observed across all subgroups with prior surgical intervention (i.e., those with VNS, resective surgery, or both). However, sample sizes were not sufficient to make statistical comparisons between those in the active or control groups with prior VNS or resective surgery, nor between the subgroups themselves (VNS vs. resective surgery vs. both vs. neither).

8.2.5.2. Longitudinal Analysis

Programming that was allowed in the Unblinded Phase included these options: remain at the core setting of 5.0 volts and 145 Hz, increase the voltage to 7.5 volts, or increase the frequency to 185 Hz. Throughout the Unblinded Phase, changes to programmed settings outside of these programming categories could be made due to adverse events. The data in Figure 9 does not suggest that increased voltage or frequency resulted in seizure frequency reduction.

8.2.6. Long Term Effectiveness

As noted in Section 8.2, the study failed to meet its primary objective (p=0.483) when all subjects were included. Open label data from the Unblinded through Long-Term Follow-up Phase were collected to provide additional safety information as well as to support efficacy established during the Blinded Phase. However, this open-label data should be viewed with caution; the following list outlines several of the primary issues associated with using the long-term data collected in this study to support the safety and effectiveness of the device:

- As stated, all data from the Unblinded and Long-term Follow-up Phases were open-label. Subjects were aware that they were receiving active stimulation.

- Following the end of the Blinded Phase, subjects could have their stimulation settings altered – during the Unblinded Phase, this was done within defined limits. However, there were no limitations for the settings during the Long-term Follow-up Phase. In addition, medications were able to be modified during the Long-term Follow-up Phase.

- As noted previously in Table 7 and Figure 3, there were 19 discontinuations following the Blinded Phase (as of June 2, 2009).

As seen in Figure 10, there did not appear to be a trend in seizure reduction over the Unblinded Phase (note, this is based only on subjects who had 70 days of diary data, which excluded 22 subjects). During the 9-month Unblinded Phase, the group as a whole (all previous control and active subjects) sustained a reduction in seizures from baseline levels. The median total seizure reduction was 40% at the end of this period (month 13 visit) as compared with baseline. Allowable changes to the programming (voltage or frequency) at month 7 and month 10 did not appear to result in appreciable improvement

in seizure reduction. At month 4-7, the active group had a 45.9% reduction, while the control group had a 34.2% reduction.

In the Unblinded Phase of the trial, the subjects that had been assigned to the active treatment still saw a much greater reduction in complex partial seizures than those who had been assigned to the control arm, even though both arms were receiving active stimulation in the Unblinded Phase (see Figure 6). This suggests that the difference in the rates of complex partial seizures may be affected by something besides the treatment received.

FDA believes that the data from the Blinded Phase of the study should be the basis for establishing the effectiveness of the device. However, the sponsor believes that seizure reduction increases over time and that the data from the blinded and open label phases of the study can therefore be used to establish the effectiveness of the device. The Panel will be asked whether the open-label data should be considered in establishing the effectiveness of the device.

9. Post-Approval Studies

NOTE TO PANELISTS: FDA's inclusion of a section/discussion on a Post-Approval study (PAS) in this executive summary should not be interpreted to mean that FDA has made a decision on the approvability of this PMA device. The presence of post-approval study plans or commitments does not in any way alter the requirements for pre-market approval and a recommendation from the Panel on whether to approve a device or not must be based on the premarket data. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The issues noted below are FDA's comments regarding potential post-approval studies should the Panel find the device approvable following its discussion and deliberations of the premarket data.

9.1. Overview of Proposed Post-Approval Study

Medtronic has proposed the following objectives for a post-approval study:

1. To collect data to characterize the long-term effectiveness of the therapy
2. To collect data to characterize long-term safety of the therapy under conditions of unrestricted access and use.
3. To collect additional product performance and adverse event data on new recipients of the therapy

Study Design and Hypotheses

The study would include two groups of patients, approximately half of which would include subjects from SANTE.

1. **SANTE Study Subjects**: Medtronic proposes that they would continue to follow the SANTE patients for 5 years post-implant. This study will evaluate therapy effectiveness, adverse events including all device-related serious adverse events, and any psychological events out to 5 years post-implant.

2. **Supplemental Subjects**: The second group would be a prospective, non-randomized, multi-center study. This study will collect additional comprehensive safety data and evaluate therapy effectiveness on new recipients of Medtronic DBS System for Epilepsy, to be followed for 5 years.

Population and Sample Size

SANTE Study Subjects

As of the time of submission of this PMA supplement (June 9, 2009), there were 94 subjects who remain active in the SANTE study. All of these subjects would be asked to participate in the SANTE post-approval study. Assuming 20% attrition per year for the remainder of the current subjects, approximately 57 subjects would be expected to be available for 5-year follow-up.

Supplemental Subjects
In an effort to supplement the safety data available from the SANTE study, Medtronic proposes that they would enroll and follow 50 new subjects for five years. In order to ensure that 5-year data would be available on 50 new subjects, Medtronic has stated that they would expect to enroll approximately 120-150 patients to account for normal attrition. The number of participating centers has not yet been determined.

The SANTE Study patients and the newly enrolled supplemental patients would both record all adverse events out to five years post-implant. Scheduled follow-ups would be the same for the two studies (semi-annual). With an overall sample size of approximately 100 patients at five years (SANTE subjects plus new subjects), there would be a 95% chance of observing at least one adverse event for which the true rate of occurrence is 3% or higher.

Data collection (Endpoints)

SANTE Study Subjects

1. **Evaluation of Long-Term Effectiveness:** Seizure frequency compared to baseline would be evaluated at yearly intervals, based on the subject's seizure diary collected for the 3-month interval prior to the conclusion of each of years 2, 3, 4 and 5.

2. **Evaluation of Long-Term Safety:** Stimulation-related adverse events and any psychological events would be collected for the duration of the post-approval study to further characterize side effects associated with stimulation of the anterior nucleus of the thalamus. All adverse events would also be collected and the SUDEP classification of all deaths would be documented.

Supplemental patients
The Supplemental Study will collect all adverse events, including those events that are thought to be related to the device, implant procedure, and/or therapy. In addition, all serious adverse events will be collected, regardless of cause, and the SUDEP classification of all deaths will be documented.

Seizure frequency compared to baseline will be evaluated at yearly intervals, based on the subject's seizure diary collected for the 3-month interval prior to the conclusion of each of years 1, 2, 3, 4 and 5.
For the purposes of this study, an adverse event would be defined as any undesirable experience (associated with signs, symptoms, illnesses, or other medical events) occurring to the patient that appears or worsens during the clinical study, and is possibly related to the device, implant procedure, and/or therapy. The SUDEP classification of all deaths would be documented. During this study, adverse event information will only be reported on a CRF in the case of death or if the event is a related to:

- The implanted components
- The implant procedure
- The stimulation therapy

Follow-up Visits and Length of Follow-up

Patents would have a clinical follow-up every six months. Adverse events would be assessed every six months and effectiveness would be evaluated annually. The total length of follow-up would be five years for all subjects. The investigator or their designee would have the ability to conduct a follow-up as an office visit.

9.2. FDA Assessment of PAS Proposal

1. The post-approval study outline provided by the sponsor did not include any study question(s) or a specific hypothesis. We believe that a hypothesis-driven study is critical to adequately evaluate effectiveness and safety performance of this device in the postmarket phase. The sponsor should revise the protocol to specify the study question(s) and provide a detailed study hypothesis.

2. The sponsor proposes enrolling 200+ patients to ensure that 100 subjects will be followed for 5 years in this PAS. 57 patients will come from the premarket study and 50 patients will be newly enrolled. However, the sponsor did not provide a sample size calculation and study power. The sample size calculation should be estimated based on a specific hypothesis that can provide sufficient study power to conduct hypothesis testing.

3. In the proposed post-approval study, there is no statistical analysis plan and no comparison group. The hypothesis-driven study with a comparison group can provides an objective approach to determine if the observed effectiveness and adverse event is within a reasonable range. We suggest that the sponsor revise the PAS protocol to include an appropriate comparison group and a detailed statistical analysis plan.

The Panel will be asked to comment on the need for a PAS (should the application be approved). Should a PAS be recommended, the Panel will be asked to comment on various elements of the proposed study design. Specifically, the Panel will be asked to discuss the following:

1. Should the system be approved, the applicant has proposed a 5-year continuation of the current pivotal study as a Post-Approval Study (PAS), as well as a second group of 50 prospective, non-randomized subjects at multiple centers.

    a. The sponsor has not proposed a comparison group (e.g., best medical therapy), and instead intends to use a patient's baseline seizure rate as a measure of sustained effectiveness. Please discuss if there is need for an active comparison group and if so, please make a recommendation on the most appropriate comparison group. Among the adverse events in the premarket study, there were a number related to depression, suicidality, cognitive changes, and seizure activity. Please discuss if an active comparison group would be needed to assess safety as well as effectiveness?

b. The SUDEP rate was 7.6 deaths per 1000 patient-years in the premarket study (Confidence Interval: 1.56, 22.08). What would be an acceptable threshold for the rate of SUDEP in the post-approval study? Which safety endpoints (in addition to SUDEP) should be evaluated in a PAS?

c. The applicant did not propose any subgroup analysis. Please discuss whether the study should include subgroups such as those who have previously failed VNS therapy or surgical ablation procedures? Are there any additional subgroups that should be included?

10. Tables

Table 1: Comparison of Kinetra and Activa PC Programming Parameters

Parameter	Kinetra Model 7426	Activa PC Model 37601
Number of clinician defined programs stored in the INS	2	2 to 16
Number of programs active at the same time	2 (1 per lead)	2 to 4 (1 or 2 per lead)
Number of defined groups	Not applicable	1 to 4
Number of programs per group	Not applicable	1 to 4
Electrode Configuration	Up to 8 electrodes (4 per lead), defined as Anode, Cathode, or OFF and the case (as Anode or OFF)	Up to 8 electrodes (4 per lead), defined as Anode, Cathode, or OFF and the case (as Anode or OFF)
Amplitude – Voltage Mode	0 – 10.5 V	0 – 10.5 V
Amplitude – Current Mode	Not applicable	0 – 25.5 mA
Pulse Rate – Voltage Mode	3 – 250 Hz	2 – 250 Hz OR 2 – 125 Hz (if using 2 programs per lead)
Pulse Rate – Current Mode	Not applicable	30 – 250 Hz OR 30 – 125 Hz (if using 2 programs per lead)
Pulse Width	60 – 450 μs	60 – 450 μs
Maximum effective rate (at a single stimulation site)	250 Hz	250 Hz
Soft Start/Stop	OFF, ON: 1, 2, 4, or 8 second ramp duration	OFF, ON: 1, 2, 4, or 8 second ramp duration
Cycling	OFF, ON: 0.1 sec to 24 hours Day Cycling also available	OFF, ON: 0.1 sec to 24 hours

(PMA cross-reference: Table 15, Volume 2)

Table 2: Testing requirements and data collection summary (Baseline Phase through Blinded Phase)

	Baseline Phase				Operative Phase			Blinded Phase				
	Week -12	Week -8	Week -4	Week 0	Device implant [a]	Pre-discharge	Week 2	Week 4 (Randomization)	Week 6	Month 2	Month 3	Month 4
Visit window (1 month = 28 days)	Within 7 days of consenting	1 mo ± 7 days after wk -12	2 mo ± 7 days after wk -12	3 mo ± 7 days after wk -12	Within 14 days of wk 0	-	2 wks ±3 days after neurostim implant	1 mo ± 7 days after neurostim implant	2 wks ±3 days after Wk 4 visit	1 mo ± 7 days after wk 4 visit	2 mo ± 7 days after wk 4 visit	3 mo ± 7 days after wk 4 visit
Informed consent	x[b]											
Inclusion and exclusion criteria	x											
Demographics	x											
Medical, surgical, & epilepsy history, most severe seizure type	x											
QOLIE-31	x							x				x
Medication monitoring [c]	x	x	x	x		x	x	x	x	x	x	x
Subject diary	x	x	x	x		x	x	x	x	x	x	x
Seizure classification	x											U x
Liverpool Seizure Severity Scale	x											x
Physical examination	x	x[d]	x[d]	x[d]		x[d]	x[d]	x	x[d]	x[d]	x[d]	x
Neurological examination	x	x[d]	x[d]	x[d]		x	x[d]	x	x[d]	x[d]	x[d]	x
Laboratory testing	x			x								
Health care resource utilization measures	x	x	x	x			x	x	x	x	x	x
Subject outcomes	x			x				x				x
Neuropsychological testing	x		x					x				x
Adverse event monitoring		x	x	x	x	x	x	x	x	x	x	x
Implant criteria				x								
MRI					x	x						
Device implant					x							
X-ray						x						
Neurostimulator monitoring						VO	VO	I/P	I	I	I	I/P
Subject satisfaction questions												x
Subject response [e]									x			x

Abbreviations: I, interrogation; MRI, magnetic resonance imagining; P, programming; QOLIE-31, Quality of Life in Epilepsy; U, update; VO, verify neurostimulator off, magnet control function disabled.

[a] The device implant starts time 0 for all subsequent visits.

[b] The week -12 visit was to be conducted within 7 days of consenting. The exception was if the subject had a VNS, and the device was to be turned off for purposes of participating in the study. In this case, the subject was to be

consented before the VNS was turned off, with the week -12 visit conducted after the VNS had been turned off at least 30 days.

[c] Rescue medications, epilepsy medications, non-epilepsy (concomitant) medications.

[d] Abbreviated examination.

[e] Subjects responded to questions about which treatment group they believed they were in.

(PMA cross-reference: Table 9.5-A, Volume 5)

Table 3: Testing requirements and data collection summary (Unblinded Phase)

Month Number	5	6	7	8	9	10	11	12	13
Visit window (1 month = 28 days)	1 mo ± 7 days after Mo 4 visit	2 mo ± 7 days after Mo 4 visit	3 mo ± 7 days after Mo 4 visit	4 mo ±7 days after Mo 4 visit	5 mo ± 7 days after Mo 4 visit	6 mo ± 7 days after Mo 4 visit	7 mo ± 7 days after Mo 4 visit	8 mo ± 7 days after Mo 4 visit	9 mo ± 7 days after Mo 4 visit
QOLIE-31			x			x			x
Medication monitoring	x	x	x	x	x	x	x	x	x
Subject diary	x	x	x	x	x	x	x	x	x
Liverpool Seizure Severity Scale			x			x			x
Physical examination	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x[a]	x
Neurological examination	x[a]	x[a]	x	x[a]	x[a]	x[a]	x[a]	x[a]	x
Health care resource utilization measures	x	x	x	x	x	x	x	x	x
Subject outcomes			x			x			x
Neuropsychological testing			x						x
Adverse event monitoring	x	x	x	x	x	x	x	x	x
Neurostimulator monitoring	I	I	I/P	I	I	I/P	I	I	I/P
Seizure classification update			x						x
Subject satisfaction questions			x			x			x

Abbreviations: I, interrogation; P, programming; QOLIE-31, Quality of Life in Epilepsy.

[a] Abbreviated examination.

(PMA cross-reference: Table 9.5-B, Volume 5)

Table 4: Testing requirements and data collection summary (Long-term Follow-up Phase)

	Monthly telephone contact	Semi-annual visits	Annual visits
Visit window (Based on month 13 visit date) (1 month = 28 days)	± 1 Week	± 3 Weeks	± 3 Weeks
QOLIE-31		x	x
Epilepsy medication monitoring		x	x
Subject diary	x	x	x
Liverpool Seizure Severity Scale		x	x
Abbreviated physical exam		x	x
Abbreviated neurological exam		x	x
Health care resource utilization measures	x	x	x
Subject outcomes		x	x
Neuropsychological testing			x
Adverse event monitoring	x	x	x
Neurostimulator monitoring		I/P	I/P
Seizure classification update			x
Subject satisfaction questions			x

Abbreviations: I, interrogation; P, programming; QOLIE-31, Quality of Life in Epilepsy.
(PMA cross-reference: Table 9.5-C, Volume 5)

Table 5: Programming Options in the SANTE Study

Study Phase	Amplitude	Pulse Width	Rate	Cycling	Electrode Polarity
Blinded Phase [a]	5 volts	90 µsec	145 Hz	1 minute on 5 minutes off	Unipolar
Unblinded Phase [b]	5 volts [c]	90 µsec	145 Hz	1 minute on 5 minutes off	Unipolar
	5 volts [c]	90 µsec	185 Hz	1 minute on 5 minutes off	Unipolar
	7.5 volts	90 µsec	145 Hz	1 minute on 5 minutes off	Unipolar
Long-Term Follow-up Phase	0 – 10.5 volts	60 – 450 µsec	3 – 250 Hz	Cycled or Continuous	Unipolar or bipolar

[a] Both the active and control groups had the same stimulation settings during the Blinded Phase. The difference is that the control group had the amplitude set to 0 V.
[b] Subjects could continue to use the Blinded Phase settings or could change to one of the other two options at Month 7 or Month 10; no other changes were allowed except in the case of adverse events.
[c] If voltage or polarity had previously changed secondary to an adverse event, it was continued at tolerated/current settings for this parameter.
(PMA cross-reference: Table 12, Volume 2)

Table 6: Adverse events (nonfatal) leading to discontinuation from study

Event causing discontinuation, by MedDRA preferred term [event classification]	Last visit in study prior to discontinuation	Additional information about reason for discontinuation	Serious?
Discontinued in Unblinded Phase (months 4-13)			
Muscle contractions involuntary [Programming/Stimulation]	Month 11	Subject elected to withdraw due to event and the system was explanted	Yes [a]
Discomfort [Neurostimulator Pocket]	Month 10	Subject elected to withdraw due to event and the system was explanted	No [b]
Implant site infection [Neurostimulator pocket]	Month 9	System explanted secondary to infection and subject did not want re-implant	Yes [a]
Implant site infection [Lead/Extension Tract]	Month 10	System explanted secondary to infection and subject did not want re-implant	Yes [a]
Discontinued in Long-term Follow-up Phase (month 13 and after)			
Implant site infection [Lead/Extension Tract]	Month 23	System explanted secondary to infection and subject did not want re-implant	Yes [a]
Cognitive disorder [Programming/Stimulation]	Month 26	Subject and caregiver elected to withdraw due to event and the system was explanted	No [b]
Psychotic disorder [New Illness/Injury]	Month 37	DSMB and investigator decision to discontinue stimulation and the system was explanted	Yes [a]
Meningitis [New Illness/Injury]	Month 30	System explanted secondary to meningitis	Yes[c]
Implant site infection [Lead/Extension/Tract]	Month 55	Leads explanted secondary to infection	Yes[c]

[a] An SAE narrative is available in Section 14.3.3.1 of the PMA.
[b] A discontinuation narrative is available in Section 14.3.3.2 of the PMA.
[c] Narrative available in Section 7.7 of 90-Day Report.
(PMA cross-reference: Table 12.5-A, Volume 5)

Table 7: Reasons for discontinuation

Phase	Reason for discontinuation	No. of subjects	% of discont.[a]	Reason details [b] (number of subjects)
Enrollment	Enrollment failure [c]	5	7.6%	Exclusionary medical condition (2)
				Low number of seizures (2)
				IQ < 70 (2)
				Subject could not differentiate between epileptic and non-epileptic events. (2)
	Withdrawal of consent by subject	4	6.1%	(4)
Baseline Phase	Enrollment failure [c]	19	28.8%	IQ < 70 (7)
				Low number of seizures or greater than 30 days seizure free (6)
				AED-related (3)
				Exclusionary labs (2)
				Subject attempted suicide after not meeting baseline seizure frequency criteria; suicide attempt is an exclusion criteria (1)
	Withdrawal of consent by subject	13	19.7%	(13)
	Physician decides that the participant should no longer participate in the study	2	3.0%	High risk for hemorrhage due to excess blood vessels in region of the target (1)
				Nickel allergy (1)
	Adverse Event	1	1.5%	New diagnosis of lymphoma (1)
	Death	1	1.5%	SUDEP (1)
	Lost to follow-up	1	1.5%	(1)
	Other	1	1.5%	Subject was emotionally labile after VNS was turned off (1)
Unblinded Phase	Device Explant	4	6.1%	Implant site infection (2)
				Discomfort (1)
				Involuntary muscle contractions (1)
	Death	1	1.5%	SUDEP (1)
LTFU: 1-2 years	Device Explant	2	3.0%	Implant site infection (1)
				Therapeutic product ineffective (1)
	Death	1	1.5%	Drowning (1)
LTFU: 2-3 years	Device Explant	2	3.0%	Cognitive disorder (1)
				Meningitis (1) [d]
	Withdrawal of consent by subject	1	1.5%	(1) [d]
LTFU: > 3 years	Device Explant	6	9.0%	Therapeutic product ineffective (4)
				Implant site infection (1) [d]
				Psychotic disorder (1)

Phase	Reason for discontinuation	No. of subjects	% of discont.[a]	Reason details [b] (number of subjects)
	Death	2[e]	3.0%	SUDEP (1)
				Completed suicide (1)
	Total	**66**	**100.0%**	

Abbreviations: AED, antiepileptic drug; discont, discontinuations; EEG, electroencephalogram; IQ, intelligence quotient; LTFU, Long-term Follow-up [Phase]; SUDEP, sudden unexplained death in epilepsy; VNS, vagus nerve stimulation/ stimulator.

[a] Percentage is calculated from the number of discontinuations in this report (n=66) versus n=63 in the PMA-S

[b] Reason details from Discontinuation CRF (Form 25), with minor edits to combine "like" reasons and for spelling/clarity.

[c] Includes not meeting entrance (inclusion and exclusion) or implant criteria.

[d] Additional discontinuation since the supplement was originally submitted

[e] As of June 2009. An additional death was reported to FDA via supplement to the IDE on January 22, 2010. The sponsor is still collecting information about the death, which occurred on January 15, 2010.

(PMA cross-reference: Table 10.1-B, Volume 5. Updated as Table 5-B in the 90-Day Update)

Table 8: Demographic and baseline characteristics – age, years with epilepsy, and baseline seizure counts

	N	Mean	Standard Deviation	Median	Minimum to maximum
Age (years)	110	36.1	11.2	36.8	18.2 to 60.8
Years with epilepsy	110	22.3	13.3	21.0	2 to 60
Baseline seizure counts	110	56.1	101.0	19.5	6 to 604

(PMA cross-reference: Table 11.2-A, Volume 5)

Table 9: Demographic and baseline characteristics – gender, number of medications, and surgery status by group (Intent-to-treat [Blinded Phase] data set)

	n (Active)	% (Active, n=54)	n (Control)	% (Control, n=55)	p-value
Gender					
Male	25	46.3%	30	54.5%	0.389
Female	29	53.7%	25	45.5%	
Number of epilepsy medications at baseline					
1	5	9.3%	6	10.9%	0.288
2	26	48.1%	28	50.9%	
3	23	42.6%	18	32.7%	
4	0	-	3	5.5%	
Surgical procedure for epilepsy					
VNS implant	21	38.9%	28	50.9%	0.389
Previous epilepsy surgery	11	20.4%	16	29.1%	0.292
Unique surgical categories					
Both a VNS and previous epilepsy surgery	6	11.1%	11	20.0%	0.511
Neither a VNS nor a previous epilepsy surgery	28	51.9%	22	40.0%	
Previous epilepsy surgery only (e.g., resection)	5	9.3%	5	9.1%	
VNS implant only	15	27.8%	17	30.9%	
Medical History					
Anxiety	10	18.5%	13	23.6%	0.640
Back pain	8	14.8%	6	10.9%	0.580
Constipation	5	9.3%	5	9.1%	1.000
Depression	28	51.9%	22	40.0%	0.251
Diarrhoea	4	7.4%	6	10.9%	0.742
Dizziness	6	11.1%	7	12.7%	1.000
Documented hypersensitivity to administered drug	19	35.2%	15	27.3%	0.413
Encephalitis	6	11.1%	0	0.0%	0.013
Epilepsy	54	100.0%	55	100.0%	1.000
Gastroesophageal reflux disease	8	14.8%	5	9.1%	0.392
Head injury	8	14.8%	7	12.7%	0.788
Headache	22	40.7%	29	52.7%	0.251
Hypersensitivity	6	11.1%	4	7.3%	0.527
Hypertension	8	14.8%	10	18.2%	0.797
Insomnia	7	13.0%	5	9.1%	0.556
Memory impairment	16	29.6%	15	27.3%	0.834
Migraine	8	14.8%	6	10.9%	0.580
Rash	0	0.0%	7	12.7%	0.013
Seasonal allergy	10	18.5%	6	10.9%	0.291
Sinus disorder	7	13.0%	5	9.1%	0.556
Tinnitus	0	0.0%	6	10.9%	0.027
Tremor	5	9.3%	7	12.7%	0.761

(PMA cross-reference: Table 14.1-B, Volume 5)

Table 10: Implanted subjects – baseline seizure types

Seizure type [a]	No. of subjects	% (N=110)
Complex partial	102	92.7%
Partial to generalized	85	77.3%
Simple partial	74	67.3%
Generalized	5	4.5%
Other	1	0.9%

[a] Subjects may experience more than one seizure type.
(PMA cross-reference: Table 11.2-E, Volume 5)

Table 11: Implanted subjects – location of seizure onset

Location of seizure onset [a]	No. of subjects	% (N=110)
Temporal lobe	66	60.0%
Frontal lobe	30	27.3%
Diffuse or multifocal	10	9.1%
Other	10	9.1%
Parietal lobe	5	4.5%
Occipital lobe	4	3.6%

[a] Subjects may have seizures from more than one onset location.
(PMA cross-reference: Table 11.2-F, Volume 5)

Table 12: Device Implant Information

	n	% (N=110)
Implant side		
Left subclavicular	37	33.6%
Right subclavicular	73	66.4%
Length of extension- left		
40 cm	5	4.5%
51 cm	101	91.8%
95 cm	4	3.6%
Length of extension- right		
40 cm	6	5.5%
51 cm	100	90.9%
95 cm	4	3.6%
Electrophysiological confirmation used during implant (not mutually exclusive)- left and right		
None	93	84.5%
Microelectrode [a]	12	10.9%
Impedance	8	7.3%
Other	1	0.9%
Lead placement confirmed intraoperatively by: (not mutually exclusive)		
None	2	1.8%
Fluoroscopy	106	96.4%
X-ray	2	1.8%
Other	1	0.9%
General anesthesia used during lead implant - left and right		
Yes	80	72.7%
No	30	27.3%
Cannula use-left		
Yes	108	98.2%
No	2	1.8%
Cannula use-right		
Yes	108	98.2%
No	2	1.8%
Cannula entered AN-T - left		
Yes	105	95.5%
No	2	1.8%
Unknown	3	2.7%
Cannula entered AN-T - right		
Yes	104	94.5%
No	3	2.7%
Unknown	3	2.7%

Abbreviations: AN-T, anterior nucleus of the thalamus; VNS, vagus nerve stimulator/stimulation.
[a] Emory University was the only center that used microelectrode recording.
(PMA cross-reference: Table 11.2-D, Volume 5)

Table 13: Protocol deviations Baseline through Unblinded Phase, excluding visit window and data collection deviations

		Phase				
Deviation category	**Deviation**	**Baseline**	**Operative**	**Blinded**	**Unblinded**	**Total**
Neuropsychological testing	Incorrect version of neuropsych test completed	13	.	7	26	46
	Neuropsych testing performed after programming change	.	.	13	22	35
	Invalid neuropsych test	.	.	.	1	1
Epilepsy medications	Epilepsy medication changed prior to Month 13 visit	.	2	7	28	37
	Exceeded rescue medication usage	3	5	4	4	16
	Incorrect dosage of epilepsy medication	1	6	1	1	9
	Temporary discontinuation of epilepsy medication for surgical risk prevention	1	.	.	.	1
Programming / stimulation	Incorrect stimulation parameters	.	1	3	14	18
	Other programming error (unrelated to stim parameters)	.	3	5	7	15
	Incorrect control magnet setting	.	5	2	4	11
	Wrong contacts activated	.	.	5	.	5
	Prolonged discontinuation of stimulation	.	.	1	4	5
Access Therapy Controller	Therapy access controller not provided to patient at week 4	.	.	8	1	9
Inclusion/exclusion [a]	Eligibility criteria not met	9	.	.	.	9
	MRI exclusion criterion not evaluable at week-12 but verified prior to implant	7	.	.	.	7

		Phase				
Deviation category	**Deviation**	**Baseline**	**Operative**	**Blinded**	**Unblinded**	**Total**
	Implant criteria not met	9	.	.	.	9
IRB/informed consent [a]	Consent form process not followed	3	.	.	1	4
	Incorrect version of consent form signed	2	.	.	.	2
Randomization/ blinding [a]	Randomization error	.	.	3	.	3
	Unblinding	.	.	.	1 [b]	1
AE reporting	AE reporting error	2	5	.	.	7
Procedures not followed	Implant procedure not followed	.	4	.	.	4
	Postoperative MRI procedure not followed	.	4	.	.	4
	Follow up procedure not followed	.	1	.	.	1
Miscellaneous	Unauthorized study personnel completed study procedure	.	1	.	.	1
	GCP not followed	.	.	.	1	1
Deviation total		**50**	**37**	**59**	**115**	**261**

Abbreviations: GCP, good clinical practice; MRI, magnetic resonance imaging.

[a] Discussed in section 10.2 of the PMA.

[b] One instance of unblinding occurred for one subject at Medtronic (no deviation case report form received). This occurred at the same time as the subject completed the Blinded Phase.

Table 14: Primary safety data sets analyzed

Data Sets Analyzed	Total n	Active n	Control n	Total Excluded
Safety – all enrolled	157	-	-	0
Safety – all implanted	110	-	-	0
Safety – all randomized	109	54	55	0
Safety – Unblinded Phase	108	-	-	0
Safety – Long-term Follow-up Phase	105	-	-	0
Safety – Long-term Follow-up Phase Year 2	105			
Safety – Long-term Follow-up Phase Year 3	102			
Safety – Long-term Follow-up Phase > Year 3	57 [a]			
SUDEP (SANTÉ study)	110	-	-	0

[a] Of the 102 subjects who had a month 25 visit, 57 subjects have completed a month 37 visit as of June 2, 2009

Table 15: Listing of subjects with Blinded Phase paraesthesia adverse events

Event classification	Verbatim	Severity	Intervention [a]	Outcome
Active Group (n=5)				
Programming/ Stimulation	Tingling over neurostimulator	Mild	None	Resolved (in 1373 days)
Programming/ Stimulation	Tingling sensation around battery	Mild	None	Ongoing
Programming/ Stimulation	Tingling sensation throughout body every 5-10 min began after randomization	Moderate	Reprogramming: Voltage decreased from 5 to 3 on day 2.	Resolved (in 139 days)
Programming/ Stimulation	Tingling over neurostimulator	Moderate	Reprogramming Voltage decreased from 5 to 4.5 on day 159, to 3.5 on day 194, and to 3.0 on day 236.	Resolved (in 264 days)
Programming/ Stimulation	Shocking pain in chest area near device.	Mild	None	Ongoing
Control Group (n=2)				
New Illness/Injury	Slight shock on neck & over device on intraclavicular region secondary to pt leaned against air conditioner frayed cord	Mild	None	Resolved (on same day)
Programming/ Stimulation	Shocking sensation at the position of the leads	Mild	None	Resolved (in 98 days)

[a] Programming interventions have been summarized. Details of the reprogramming interventions are provided in appendix 16.4.11.1. of the PMA.
[b] Randomization occurred at the week 4 visit.

Table 16: Subjects at 2 years with a worsening of 50% seizure frequency, as compared with baseline, and AED and stimulation status

Overall: % change at 2 years	Simple: % change at 2 years	Complex: % change at 2 years	AED and stimulation settings at 2 years
73.7%	88.6%	-100%	AED: Decreased AEDs (dose decrease in 1 medication) Stimulation settings: 5.0 V, 90 µs, 145 Hz and cycled stimulation (1 min on, 5 off)
194.9%	268.9%	0.1%	AED: Combination AED (started 1 medication and stopped 1 medication) Stimulation settings: 7.5 V, 90 µs and 145 Hz, and continuous stimulation
266.0%	626.1%	-65.3%	AED: Decreased AEDs (stopped 1 medication) Stimulation settings: 3.5-5 V, 90 µs, 100-185 Hz, and cycled stimulation (1 min on, 5 min off)

Abbreviations: AED, antiepileptic drugs; complex, complex partial seizures; simple, simple partial seizures.

Table 17: Summary of adverse events by organ class, Operative through Unblinded Phases

System Organ Class	Preferred Term	Events (Serious)	Subjects with an Event (n=110)
Infections and infestations	Nasopharyngitis	27	22 (20.0%)
	Upper respiratory tract infection	20	15 (13.6%)
	Implant site infection	11 (8)	10 (9.1%)
	Sinusitis	9	8 (7.3%)
	Influenza	8	7 (6.4%)
	Bronchitis	5	5 (4.5%)
	Otitis media	4	4 (3.6%)
	Urinary tract infection	4	4 (3.6%)
	Tooth infection	3	3 (2.7%)
	Vaginal mycosis	3	2 (1.8%)
	Dental caries	2	2 (1.8%)
	Gastroenteritis	2	2 (1.8%)
	Hordeolum	2	2 (1.8%)
	Localised infection	2	2 (1.8%)
	Pneumonia	2	2 (1.8%)
	Viral infection	2	2 (1.8%)
	Gastroenteritis viral	2	1 (0.9%)
	Meningitis	1 (1)	1 (0.9%)
	Urosepsis	1 (1)	1 (0.9%)
	Catheter related infection	1	1 (0.9%)
	Cellulitis	1	1 (0.9%)
	Cystitis	1	1 (0.9%)
	Folliculitis	1	1 (0.9%)
	Gingival infection	1	1 (0.9%)
	Herpes simplex	1	1 (0.9%)
	Infected insect bite	1	1 (0.9%)
	Lower respiratory tract infection	1	1 (0.9%)
	Onychomycosis	1	1 (0.9%)
	Otitis externa	1	1 (0.9%)
	Respiratory tract infection	1	1 (0.9%)
	Skin infection	1	1 (0.9%)
	Tinea pedis	1	1 (0.9%)
	Tooth abscess	1	1 (0.9%)
	Vaginal infection	1	1 (0.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Skin papilloma	3	3 (2.7%)
Blood and lymphatic system disorders	Lymphadenopathy	1	1 (0.9%)
Immune system disorders	Hypersensitivity	3	3 (2.7%)
	Seasonal allergy	3	3 (2.7%)
Endocrine disorders	Hypothyroidism	1	1 (0.9%)
Metabolism and nutrition disorders	Hyponatraemia	3	3 (2.7%)
	Decreased appetite	1	1 (0.9%)
	Diabetes mellitus	1	1 (0.9%)
	Hyperglycaemia	1	1 (0.9%)
Psychiatric disorders	Depression	22 (1)	22 (20.0%)
	Anxiety	9 (1)	8 (7.3%)

System Organ Class	Preferred Term	Events (Serious)	Subjects with an Event (n=110)
	Confusional state	7	5 (4.5%)
	Agitation	4	4 (3.6%)
	Deja vu	4	4 (3.6%)
	Insomnia	4	4 (3.6%)
	Thinking abnormal	3	3 (2.7%)
	Hallucination	2	2 (1.8%)
	Initial insomnia	2	2 (1.8%)
	Nervousness	2	2 (1.8%)
	Panic attack	2	2 (1.8%)
	Sleep disorder	2	2 (1.8%)
	Stress	2	2 (1.8%)
	Conversion disorder	1 (1)	1 (0.9%)
	Depression suicidal	1 (1)	1 (0.9%)
	Tension	1 (1)	1 (0.9%)
	Anger	1	1 (0.9%)
	Bruxism	1	1 (0.9%)
	Disorientation	1	1 (0.9%)
	Emotional disorder	1	1 (0.9%)
	Hallucination, visual	1	1 (0.9%)
	Mental disorder	1	1 (0.9%)
	Obsessive-compulsive disorder	1	1 (0.9%)
	Psychotic disorder	1	1 (0.9%)
	Suicidal ideation	1	1 (0.9%)
Nervous system disorders	Headache	29	23 (20.9%)
	Memory impairment	22	22 (20.0%)
	Paraesthesia	24	21 (19.1%)
	Partial seizures with secondary generalisation	18 (6)	16 (14.5%)
	Complex partial seizures	16 (2)	14 (12.7%)
	Simple partial seizures	16	14 (12.7%)
	Dizziness	13	10 (9.1%)
	Sensory disturbance	9	9 (8.2%)
	Hypoaesthesia	6	6 (5.5%)
	Status epilepticus	4 (3)	4 (3.6%)
	Somnolence	4	4 (3.6%)
	Grand mal convulsion	4	3 (2.7%)
	Burning sensation	2	2 (1.8%)
	Coordination abnormal	2	2 (1.8%)
	Tremor	4	3 (2.7%)
	Muscle contractions involuntary	1 (1)	1 (0.9%)
	Transient ischaemic attack	1 (1)	1 (0.9%)
	Unresponsive to verbal stimuli	1 (1)	1 (0.9%)
	Convulsion	2	2 (1.8%)
	Disturbance in attention	1	1 (0.9%)
	Dyskinesia	1	1 (0.9%)
	Essential tremor	1	1 (0.9%)
	Facial palsy	1	1 (0.9%)
	Haemorrhage intracranial	1	1 (0.9%)
	Intention tremor	1	1 (0.9%)
	Intraventricular haemorrhage	1	1 (0.9%)
	Lethargy	1	1 (0.9%)

System Organ Class	Preferred Term	Events (Serious)	Subjects with an Event (n=110)
	Mental impairment	1	1 (0.9%)
	Neuralgia	1	1 (0.9%)
	Neuropathy peripheral	1	1 (0.9%)
	Nystagmus	1	1 (0.9%)
	Postictal headache	1	1 (0.9%)
	Sciatica	1	1 (0.9%)
	Syncope	1	1 (0.9%)
	Syncope vasovagal	1	1 (0.9%)
Eye disorders	Vision blurred	2	2 (1.8%)
	Visual disturbance	2	2 (1.8%)
	Blindness transient	1	1 (0.9%)
	Diplopia	1	1 (0.9%)
	Extraocular muscle paresis	1	1 (0.9%)
	Eye pain	1	1 (0.9%)
	Eyelid disorder	1	1 (0.9%)
	Lacrimation increased	1	1 (0.9%)
Ear and labyrinth disorders	Ear pain	2	2 (1.8%)
	Hypoacusis	2	2 (1.8%)
	Tinnitus	2	2 (1.8%)
	Cerumen impaction	1	1 (0.9%)
	External ear disorder	1	1 (0.9%)
Cardiac disorders	Cardiac flutter	1	1 (0.9%)
	Tachycardia	1	1 (0.9%)
Vascular disorders	Hypertension	3	3 (2.7%)
	Hot flush	1	1 (0.9%)
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	5	5 (4.5%)
	Cough	2	2 (1.8%)
	Nasal congestion	2	2 (1.8%)
	Dyspnoea	1	1 (0.9%)
	Epistaxis	1	1 (0.9%)
	Painful respiration	1	1 (0.9%)
	Sinus congestion	1	1 (0.9%)
	Sleep apnoea syndrome	1	1 (0.9%)
	Vocal cord disorder	1	1 (0.9%)
Gastrointestinal disorders	Vomiting	4 (2)	4 (3.6%)
	Nausea	4	4 (3.6%)
	Gastrooesophageal reflux disease	2 (1)	2 (1.8%)
	Abdominal pain	2	2 (1.8%)
	Constipation	2	2 (1.8%)
	Hypoaesthesia oral	2	2 (1.8%)
	Abdominal pain lower	1	1 (0.9%)
	Abdominal pain upper	1	1 (0.9%)
	Acquired oesophageal web	1	1 (0.9%)
	Colitis ulcerative	1	1 (0.9%)
	Diarrhoea	1	1 (0.9%)
	Haemorrhoids	1	1 (0.9%)
	Hiatus hernia	1	1 (0.9%)
	Tooth impacted	1	1 (0.9%)
	Tooth loss	1	1 (0.9%)
Skin and	Dermatitis contact	6	4 (3.6%)

System Organ Class	Preferred Term	Events (Serious)	Subjects with an Event (n=110)
subcutaneous tissue disorders	Acne	3	3 (2.7%)
	Pruritus	2	2 (1.8%)
	Ecchymosis	2	1 (0.9%)
	Blister	1	1 (0.9%)
	Dermal cyst	1	1 (0.9%)
	Dermatitis	1	1 (0.9%)
	Nail disorder	1	1 (0.9%)
	Swelling face	1	1 (0.9%)
Musculoskeletal and connective tissue disorders	Back pain	7	7 (6.4%)
	Shoulder pain	5	5 (4.5%)
	Arthralgia	4	4 (3.6%)
	Musculoskeletal stiffness	3	3 (2.7%)
	Pain in extremity	3	3 (2.7%)
	Chest wall pain	1	1 (0.9%)
	Coccydynia	1	1 (0.9%)
	Exostosis	1	1 (0.9%)
	Muscle tightness	1	1 (0.9%)
	Muscle twitching	1	1 (0.9%)
	Neck pain	1	1 (0.9%)
	Osteoporosis	1	1 (0.9%)
	Pain in jaw	1	1 (0.9%)
Renal and urinary disorders	Renal failure acute	1 (1)	1 (0.9%)
Reproductive system and breast disorders	Menorrhagia	2	2 (1.8%)
	Benign prostatic hyperplasia	1	1 (0.9%)
	Dysfunctional uterine bleeding	1	1 (0.9%)
	Erectile dysfunction	1	1 (0.9%)
	Premenstrual syndrome	1	1 (0.9%)
	Vaginal haemorrhage	1	1 (0.9%)
Congenital, familial and genetic disorders	Peroneal muscular atrophy	1	1 (0.9%)
General disorders and administration site conditions	Implant site pain	15	13 (11.8%)
	Discomfort	9	8 (7.3%)
	Implant site inflammation	5	5 (4.5%)
	Pain	3	3 (2.7%)
	Implant site effusion	3	3 (2.7%)
	Chest pain	1	1 (0.9%)
	Fatigue	2	2 (1.8%)
	Implant site oedema	2	2 (1.8%)
	Tenderness	2	2 (1.8%)
	Face oedema	2	1 (0.9%)
	Pyrexia	1 (1)	1 (0.9%)
	Sudden unexplained death in epilepsy	1 (1)	1 (0.9%)
	Asthenia	1	1 (0.9%)
	Chills	1	1 (0.9%)
	Facial pain	1	1 (0.9%)
	Gait disturbance	1	1 (0.9%)
	Implant site fibrosis	1	1 (0.9%)
	Implant site scar	1	1 (0.9%)
	Implant site swelling	1	1 (0.9%)
	Implant site warmth	1	1 (0.9%)

System Organ Class	Preferred Term	Events (Serious)	Subjects with an Event (n=110)
	Oedema	1	1 (0.9%)
	Oedema peripheral	1	1 (0.9%)
	Ulcer	1	1 (0.9%)
Investigations	Blood pressure increased	2	2 (1.8%)
	Anticonvulsant drug level decreased	1	1 (0.9%)
	Blood cholesterol increased	1	1 (0.9%)
	Blood magnesium decreased	1	1 (0.9%)
	Heart rate irregular	1	1 (0.9%)
	Weight decreased	1	1 (0.9%)
Injury, poisoning and procedural complications	Injury	34	19 (17.3%)
	Anticonvulsant toxicity	21	19 (17.3%)
	Contusion	17	16 (14.5%)
	Excoriation	10	8 (7.3%)
	Head injury	9	8 (7.3%)
	Post procedural pain	7 (2)	7 (6.4%)
	Laceration	7	7 (6.4%)
	Postoperative fever	6 (2)	5 (4.5%)
	Skin laceration	6	5 (4.5%)
	Drug toxicity	5 (1)	5 (4.5%)
	Documented hypersensitivity to administered drug	5	5 (4.5%)
	Thermal burn	5	5 (4.5%)
	Mouth injury	5	3 (2.7%)
	Procedural complication	4	3 (2.7%)
	Incision site complication	3	3 (2.7%)
	Joint sprain	3	3 (2.7%)
	Wrist fracture	2 (1)	2 (1.8%)
	Fall	2	2 (1.8%)
	Limb injury	2	2 (1.8%)
	Arthropod bite	1	1 (0.9%)
	Back injury	1	1 (0.9%)
	Clavicle fracture	1	1 (0.9%)
	Device malfunction	1	1 (0.9%)
	Dural tear	1	1 (0.9%)
	Ear abrasion	1	1 (0.9%)
	Face injury	1	1 (0.9%)
	Heat exhaustion	1	1 (0.9%)
	Incision site haemorrhage	1	1 (0.9%)
	Intra-uterine contraceptive device expelled	1	1 (0.9%)
	Joint injury	1	1 (0.9%)
	Lower limb fracture	1	1 (0.9%)
	Medical device complication	1	1 (0.9%)
	Muscle injury	1	1 (0.9%)
	Neck injury	1	1 (0.9%)
	Periorbital hematoma	1	1 (0.9%)
	Post procedural complication	1	1 (0.9%)
	Post procedural haemorrhage	1	1 (0.9%)
	Subdural haematoma	1	1 (0.9%)
	Tongue injury	1	1 (0.9%)
	Tooth injury	1	1 (0.9%)
	Upper limb fracture	1	1 (0.9%)

System Organ Class	Preferred Term	Events (Serious)	Subjects with an Event (n=110)
	Wound dehiscence	1	1 (0.9%)
Surgical and medical procedures	Wound drainage	1 (1)	1 (0.9%)
	Post procedural drainage	1	1 (0.9%)
Medtronic	Lead(s) not within target	12 (12)	9 (8.2%)
	Extension fracture	6	4 (3.6%)
	Extension migration/dislodgment	4	3 (2.7%)
	Neurostimulator migration	3	3 (2.7%)
	High impedance	3	2 (1.8%)
	Lead fracture	2	2 (1.8%)
	Set screws not adequately secured	1 (1)	1 (0.9%)
	Lead migration/dislodgment	1	1 (0.9%)
	Adverse Event Total	**808 (55)**	**109 (99.1%)**

Table 18: Summary of adverse events by organ class, long-term follow-up phase

System Organ Class	Preferred Term	Events (Serious)	Subjects with an Event (n=110)
Infections and infestations	Nasopharyngitis	35	26 (24.8%)
	Upper respiratory tract infection	21	16 (15.2%)
	Sinusitis	12	10 (9.5%)
	Influenza	10	10 (9.5%)
	Urinary tract infection	8	8 (7.6%)
	Gastroenteritis viral	7	6 (5.7%)
	Bronchitis	6	4 (3.8%)
	Implant site infection	5 (4)	4 (3.8%)
	Cellulitis	4 (1)	4 (3.8%)
	Ear infection	4	4 (3.8%)
	Pharyngitis streptococcal	3	3 (2.9%)
	Gastroenteritis	3	2 (1.9%)
	Tooth infection	3	2 (1.9%)
	Vaginal mycosis	3	2 (1.9%)
	Bronchitis acute	2	2 (1.9%)
	Eye infection	2	2 (1.9%)
	Otitis media	2	2 (1.9%)
	Respiratory tract infection	2	2 (1.9%)
	Tonsillitis	2	2 (1.9%)
	Tooth abscess	2	1 (1.0%)
	Skin infection	1 (1)	1 (1.0%)
	Body tinea	1	1 (1.0%)
	Cystitis	1	1 (1.0%)
	Dental caries	1	1 (1.0%)
	Folliculitis	1	1 (1.0%)
	Hepatitis C	1	1 (1.0%)
	Herpes zoster	1	1 (1.0%)
	Hordeolum	1	1 (1.0%)
	Kidney infection	1	1 (1.0%)
	Lobar pneumonia	1	1 (1.0%)
	Localised infection	1	1 (1.0%)
	Lyme disease	1	1 (1.0%)
	Pharyngitis	1	1 (1.0%)
	Pneumonia	1	1 (1.0%)
	Pneumonia primary atypical	1	1 (1.0%)
	Pulpitis dental	1	1 (1.0%)
	Rhinovirus infection	1	1 (1.0%)
	Tinea cruris	1	1 (1.0%)
	Vaginal infection	1	1 (1.0%)
	Vaginitis bacterial	1	1 (1.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Skin papilloma	2	2 (1.9%)
	Basal cell carcinoma	1	1 (1.0%)
	Haemangioma	1	1 (1.0%)
	Nasal neoplasm benign	1	1 (1.0%)
Blood and lymphatic system disorders	Anaemia	3	3 (2.9%)
Immune system disorders	Seasonal allergy	4	4 (3.8%)
	Hypersensitivity	2	2 (1.9%)
	Allergy to arthropod sting	1	1 (1.0%)

System Organ Class	Preferred Term	Events (Serious)	Subjects with an Event (n=110)
Endocrine disorders	Goitre	2	2 (1.9%)
	Hypothyroidism	1	1 (1.0%)
Metabolism and nutrition disorders	Diabetes mellitus	2 (1)	2 (1.9%)
	Hypokalaemia	2 (1)	2 (1.9%)
	Hyponatraemia	2 (1)	2 (1.9%)
	Dehydration	2	2 (1.9%)
	Hypercholesterolaemia	2	2 (1.9%)
	Hyperlipidaemia	1	1 (1.0%)
Psychiatric disorders	Depression	13	13 (12.4%)
	Insomnia	9	8 (7.6%)
	Anxiety	7	6 (5.7%)
	Psychotic disorder	2 (2)	2 (1.9%)
	Suicidal ideation	2 (2)	2 (1.9%)
	Irritability	2	2 (1.9%)
	Completed suicide	1 (1)	1 (1.0%)
	Conversion disorder	1 (1)	1 (1.0%)
	Suicide attempt	1 (1)	1 (1.0%)
	Abnormal dreams	1	1 (1.0%)
	Aggression	1	1 (1.0%)
	Anger	1	1 (1.0%)
	Confusional state	1	1 (1.0%)
	Delusion	1	1 (1.0%)
	Depression suicidal	1	1 (1.0%)
	Dysphemia	1	1 (1.0%)
	Epileptic psychosis	1	1 (1.0%)
	Hallucination	1	1 (1.0%)
	Homicidal ideation	1	1 (1.0%)
	Intentional self-injury	1	1 (1.0%)
	Panic attack	1	1 (1.0%)
	Self injurious behaviour	1	1 (1.0%)
	Stress	1	1 (1.0%)
	Tension	1	1 (1.0%)
Nervous system disorders	Complex partial seizures	26 (2)	19 (18.1%)
	Headache	17	15 (14.3%)
	Partial seizures with secondary generalisation	20 (6)	14 (13.3%)
	Simple partial seizures	16 (2)	14 (13.3%)
	Paraesthesia	12	10 (9.5%)
	Memory impairment	8	8 (7.6%)
	Tremor	6	5 (4.8%)
	Convulsion	4 (1)	4 (3.8%)
	Dizziness	3	3 (2.9%)
	Dyskinesia	3	3 (2.9%)
	Burning sensation	2	2 (1.9%)
	Grand mal convulsion	2	2 (1.9%)
	Lethargy	2	2 (1.9%)
	Sinus headache	2	2 (1.9%)
	Somnolence	2	2 (1.9%)
	Neuralgia	2	1 (1.0%)
	Epilepsy	1 (1)	1 (1.0%)
	Status epilepticus	1 (1)	1 (1.0%)

System Organ Class	Preferred Term	Events (Serious)	Subjects with an Event (n=110)
	Ageusia	1	1 (1.0%)
	Balance disorder	1	1 (1.0%)
	Carpal tunnel syndrome	1	1 (1.0%)
	Cognitive disorder	1	1 (1.0%)
	Coordination abnormal	1	1 (1.0%)
	Dysarthria	1	1 (1.0%)
	Hydrocephalus	1	1 (1.0%)
	Hypersomnia	1	1 (1.0%)
	Intraventricular haemorrhage	1	1 (1.0%)
	Migraine	1	1 (1.0%)
	Myoclonus	1	1 (1.0%)
	Postictal state	1	1 (1.0%)
	Sciatica	1	1 (1.0%)
	Sensory disturbance	1	1 (1.0%)
	Tension headache	1	1 (1.0%)
Eye disorders	Vision blurred	2	2 (1.9%)
	Visual disturbance	2	1 (1.0%)
	Blepharospasm	1	1 (1.0%)
	Diplopia	1	1 (1.0%)
	Eye haemorrhage	1	1 (1.0%)
	Eye pain	1	1 (1.0%)
	Macular degeneration	1	1 (1.0%)
Ear and labyrinth disorders	Ear pain	3	3 (2.9%)
	Vertigo	3	2 (1.9%)
	Ear discomfort	2	2 (1.9%)
	Tinnitus	2	2 (1.9%)
	Tympanic membrane perforation	2	2 (1.9%)
Cardiac disorders	Angina pectoris	1	1 (1.0%)
	Palpitations	1	1 (1.0%)
Vascular disorders	Hypertension	3	3 (2.9%)
	Haematoma	1	1 (1.0%)
Respiratory, thoracic and mediastinal disorders	Pharyngolaryngeal pain	4	4 (3.8%)
	Respiratory distress	1 (1)	1 (1.0%)
	Asthma	1	1 (1.0%)
	Cough	1	1 (1.0%)
	Sleep apnoea syndrome	1	1 (1.0%)
	Upper respiratory tract congestion	1	1 (1.0%)
Gastrointestinal disorders	Diarrhoea	7	6 (5.7%)
	Gastrooesophageal reflux disease	3	3 (2.9%)
	Haemorrhoids	3	3 (2.9%)
	Tooth fracture	3	3 (2.9%)
	Constipation	2	2 (1.9%)
	Nausea	2	2 (1.9%)
	Tooth disorder	2	2 (1.9%)
	Toothache	2	2 (1.9%)
	Vomiting	2	2 (1.9%)
	Abdominal discomfort	1	1 (1.0%)
	Abdominal pain	1	1 (1.0%)
	Abdominal pain upper	1	1 (1.0%)
	Dyspepsia	1	1 (1.0%)
	Dysphagia	1	1 (1.0%)

System Organ Class	Preferred Term	Events (Serious)	Subjects with an Event (n=110)
	Epigastric discomfort	1	1 (1.0%)
	Food poisoning	1	1 (1.0%)
	Hiatus hernia	1	1 (1.0%)
	Lip blister	1	1 (1.0%)
	Mouth ulceration	1	1 (1.0%)
Skin and subcutaneous tissue disorders	Rash	7	7 (6.7%)
	Dermatitis contact	4	4 (3.8%)
	Ingrowing nail	3	3 (2.9%)
	Acne	1	1 (1.0%)
	Dermatitis	1	1 (1.0%)
	Dry skin	1	1 (1.0%)
	Ecchymosis	1	1 (1.0%)
	Eczema	1	1 (1.0%)
	Heat rash	1	1 (1.0%)
	Hyperhidrosis	1	1 (1.0%)
	Hyperkeratosis	1	1 (1.0%)
	Lichen planus	1	1 (1.0%)
	Seborrhoeic dermatitis	1	1 (1.0%)
	Urticaria	1	1 (1.0%)
Musculoskeletal and connective tissue disorders	Back pain	10 (1)	9 (8.6%)
	Arthralgia	7	7 (6.7%)
	Pain in extremity	7	6 (5.7%)
	Shoulder pain	5	4 (3.8%)
	Neck pain	3	3 (2.9%)
	Muscle spasms	2	2 (1.9%)
	Muscle twitching	2	2 (1.9%)
	Osteoarthritis	2	2 (1.9%)
	Bursitis	1	1 (1.0%)
	Chest wall pain	1	1 (1.0%)
	Ganglion	1	1 (1.0%)
	Muscle tightness	1	1 (1.0%)
	Osteopenia	1	1 (1.0%)
	Pain in jaw	1	1 (1.0%)
	Plantar fasciitis	1	1 (1.0%)
	Tendonitis	1	1 (1.0%)
	Trismus	1	1 (1.0%)
Renal and urinary disorders	Cystitis interstitial	3	2 (1.9%)
	Dysuria	2	2 (1.9%)
	Nephrolithiasis	1	1 (1.0%)
Pregnancy, puerperium and perinatal conditions	Uterine contractions abnormal	1 (1)	1 (1.0%)
	Blighted ovum	1	1 (1.0%)
Reproductive system and breast disorders	Breast pain	1	1 (1.0%)
	Fibrocystic breast disease	1	1 (1.0%)
	Pelvic pain	1	1 (1.0%)
	Polycystic ovaries	1	1 (1.0%)
Congenital, familial and genetic disorders	Peroneal muscular atrophy	1	1 (1.0%)
	Pigmented naevus	1	1 (1.0%)
General disorders and administration site conditions	Implant site pain	9	9 (8.6%)
	Therapeutic product ineffective	7 (2)	7 (6.7%)
	Chest pain	5	5 (4.8%)

System Organ Class	Preferred Term	Events (Serious)	Subjects with an Event (n=110)
	Implant site inflammation	3 (1)	3 (2.9%)
	Discomfort	3	3 (2.9%)
	Pain	3	3 (2.9%)
	Fatigue	2	2 (1.9%)
	Implant site effusion	2	2 (1.9%)
	Drowning	1 (1)	1 (1.0%)
	Pyrexia	1 (1)	1 (1.0%)
	Sudden unexplained death in epilepsy	1 (1)	1 (1.0%)
	Asthenia	1	1 (1.0%)
	Circadian rhythm sleep disorder	1	1 (1.0%)
	Gait disturbance	1	1 (1.0%)
	Hyperthermia	1	1 (1.0%)
	Implant site erosion	1	1 (1.0%)
	Implant site haematoma	1	1 (1.0%)
	Implant site pruritus	1	1 (1.0%)
	Oedema peripheral	1	1 (1.0%)
Investigations	Anticonvulsant drug level below therapeutic	1	1 (1.0%)
	Anticonvulsant drug level decreased	1	1 (1.0%)
	Blood cholesterol increased	1	1 (1.0%)
	Blood urine present	1	1 (1.0%)
	White blood cell count decreased	1	1 (1.0%)
Injury, poisoning and procedural complications	Anticonvulsant toxicity	46 (3)	25 (23.8%)
	Injury	28	21 (20.0%)
	Skin laceration	17 (1)	15 (14.3%)
	Laceration	7	7 (6.7%)
	Limb injury	7	7 (6.7%)
	Excoriation	10	6 (5.7%)
	Drug toxicity	9	6 (5.7%)
	Head injury	7	6 (5.7%)
	Joint sprain	5	5 (4.8%)
	Contusion	5	4 (3.8%)
	Arthropod sting	4	3 (2.9%)
	Mouth injury	3	2 (1.9%)
	Animal bite	2	2 (1.9%)
	Burns second degree	2	2 (1.9%)
	Documented hypersensitivity to administered drug	2	2 (1.9%)
	Fall	2	2 (1.9%)
	Hand fracture	2	2 (1.9%)
	Muscle strain	2	2 (1.9%)
	Ankle fracture	1	1 (1.0%)
	Back injury	1	1 (1.0%)
	Clavicle fracture	1	1 (1.0%)
	Concussion	1	1 (1.0%)
	Epicondylitis	1	1 (1.0%)
	Eye injury	1	1 (1.0%)
	Facial bones fracture	1	1 (1.0%)
	Foot fracture	1	1 (1.0%)
	Forearm fracture	1	1 (1.0%)
	Foreign body in eye	1	1 (1.0%)
	Foreign body trauma	1	1 (1.0%)

System Organ Class	Preferred Term	Events (Serious)	Subjects with an Event (n=110)
	Joint injury	1	1 (1.0%)
	Lower limb fracture	1	1 (1.0%)
	Muscle injury	1	1 (1.0%)
	Thermal burn	1	1 (1.0%)
	Tongue injury	1	1 (1.0%)
	Upper limb fracture	1	1 (1.0%)
Surgical and medical procedures	Therapeutic procedure	1	1 (1.0%)
	Wisdom teeth removal	1	1 (1.0%)
Social circumstances	Menopause	1	1 (1.0%)
Medtronic	Extension fracture	3 (1)	2 (1.9%)
	High impedance	1	1 (1.0%)
	Neurostimulator migration	1	1 (1.0%)
	Set screws not adequately secured	1	1 (1.0%)
	Adverse Event Total	**776 (43)**	**102 (97.1%)**

Table 19: Summary of deaths and SUDEP determination

Study phase at time of death (last study visit)	MedDRA preferred term	Circumstances of death	Autopsy performed?	DSMB SUDEP determination	Stimulation ON at time of death?
Baseline (Week -4)	Sudden unexplained death in epilepsy	Subject found dead, next to her bed	No	Probable SUDEP [a]	NA
Unblinded (Month 7)	Sudden unexplained death in epilepsy	Subject found unresponsive in bed, did not respond to resuscitation efforts	Yes	Definite SUDEP	Yes
Long-term Follow-up (Month 50)	Sudden unexplained death in epilepsy	Subject found dead in bed	Yes	Definite SUDEP	No [b]
Long-term Follow-up (Month 20)	Drowning	Subject found dead in bathtub	No	Possible SUDEP	Yes
Long-term Follow-up (Month 46)	Completed Suicide	Subject committed suicide by gunshot	No	Not SUDEP	No [c]
Long-term Follow-up (Month 72)	Pending [d]	The subject was found unresponsive at home and was on life support for 3 days.	No	Pending [d]	Yes

Abbreviations: NA, not applicable; SUDEP, sudden unexplained death in epilepsy.
[a] Not included in SUDEP calculations, as subject was not implanted and did not receive stimulation.
[b] Stimulation had been off for a month secondary to a seizure-related serious adverse event.
[c] Stimulation had been off for 3 weeks due to battery depletion.
[d] Event occurred after the database cutoff for this report (death reported to Medtronic in January 2010).
(PMA cross-reference: Table 12.4-A, Volume 5)

Table 20: SUDEP Summary

	No. of SUDEP [a]	Approximate years with stimulation	SUDEP rate /1000 subject-years	95% Poisson Confidence Interval (/1000 subject-years)
Definite	2	397 yrs	5.0 / 1000 yrs	[0.61, 18.20]
Probable	0	397 yrs	0.0 / 1000 yrs	[0.00, 9.29]
Possible	1	397 yrs	2.5 / 1000 yrs	[0.06, 14.03]
Total	3	397 yrs	7.6 / 1000 yrs	[1.56, 22.08]

Abbreviations: SUDEP, sudden unexplained death in epilepsy

[a] Number of years with stimulation based on the Sante study, combined data from three pilot centers participating in the Stimulation for Epilepsy Long-Term Follow-up study, and two pilot centers not participating in the follow-up study.

(PMA Cross Reference: 90-Day Report, Section X, Table 19, page 1-121.)

Table 21: Review of suicidality adverse events in implanted subjects

MedDRA PT [Verbatim]	Hx of depression or suicide	Epil meds at time of event [a]	Serious	Severity	Outcome	Phase
Suicide attempt [Attempted suicide]	No	lev, phen	Yes: inpatient hospitalization	Severe	Resolved (in 69 days)	LTFU
Depression suicidal [Depression with suicidal ideations]	No	lam[b], ox[b], top	No	Mild	Ongoing	LTFU
Intentional self-injury [Suicide gesture]	Yes	clon, lev, zon	No	Mild	Resolved (in 45 days)	LTFU
Suicidal ideation [Suicidal ideations]	Yes	ox, phen, zon	No	Moderate	Resolved (in 5 days)	Blinded (Active)
Suicidal ideation [Suicide ideation]	Yes	lam, top, zon	Yes: Inpatient hospitalization	Severe	Resolved (in 91 days)	LTFU
Completed suicide [Suicide]	Yes	carb	Yes: Death	Severe	Death	LTFU
Suicidal ideation [Suicidal ideation]	Yes	lev, fel	Yes: Inpatient hospitalization	Moderate	Resolved (in 21 days)	LTFU
Depression suicidal [Depression with suicidal ideation]	Yes	lam, lev	Yes: Inpatient hospitalization	Severe	Ongoing	Unblinded

Abbreviations: epil, epilepsy; hx, history; LTFU, Long-term Follow-up [Phase]; meds, medications; PT, preferred term.

[a] Medication code: carb = carbamazepine, clon = clonazepam, fel = felbamate, lam = lamotrigine, lev = levetiracetam, ox = oxcarbamazepine, phen = phenytoin, top = topirimate, zon = zonisamide.

[b] Medication change in week prior to event.

Table 22: Listing of the intracranial hemorrhage events

Phase reported	MedDRA preferred term [verbatim]	Details of event	Clinical manifestations
Operative	Subdural hematoma [Subdural hematoma along B convexities]	Noted on postoperative MRI the day of system implant	None
	Hemorrhage intracranial [Blood at left frontal cortex lead entry point.]	Noted on postoperative MRI 1 day after original system implant.	None
	Post procedural hemorrhage [Minimal blood at left lead entry point]	Noted 1 day after system implant on postoperative MRI	None
	Intraventricular hemorrhage [Hemorrhage in the right lateral ventricle 7 x 1.9 mm; small amount of hemorrhage within the occipital horns of the lateral ventricles.]	Noted the day of system implant on a CT scan after increased seizures	None
LTFU	Intraventricular hemorrhage [Interventricular hemorrhage in the right occipital porencephalic cyst [a]]	Subject underwent a complete system explant due to device-related infection. Later that day, the subject had a seizure-related fall and a CT scan was performed.	None

Abbreviations: MRI, magnetic resonance imaging. LTFU, long-term follow-up
[a] Pre-existing cyst.
(PMA cross-reference: Table 12.5-C, Volume 5)

Table 23: Listing of status epilepticus adverse events

Phase reported	Convulsive or nonconvulsive	Serious?	Timing of event
Operative	Non-convulsive	No [a]	Occurred the day of the original implant procedure
	Non-convulsive	Yes	1 week after original implant procedure.
Blinded	Non-convulsive	Yes	Month 2 (active subject)
Unblinded	Non-convulsive	Yes	Occurred the day of the month 4 visit, when stimulation was turned on (control subject) [b]
LTFU [c]	Convulsive	Yes	Between month 49 and 50

Abbreviations: LTFU, Long-term Follow-up [Phase].
[a] Was already in hospital for the implant procedure, and the event did not cause prolongation of hospital stay, thus did not meet serious criteria.
[b] Assessed by the investigator to be device-related (specifically to stimulation).
[c] Stimulation had been off for approximately a year as subject wanted to try ketogenic diet for seizures.
(PMA cross-reference: Table 12.5-D, Volume 5)

Table 24: Number of subjects with a serious adverse event by treatment group in the Blinded Phase (Safety – all randomized data set)

Preferred term	Active (n=54)		Control (n=55)	
	No of subjects (%) with SAE	[severity of event]	No of subjects (%) with SAE	[severity of event]
Implant site infection	.		2 (3.6%)	[severe] [moderate]
Complex partial seizures	.		1 (1.8%)	[severe]
Depression	1 (1.9%)	[moderate]	.	
Partial seizures with secondary generalization	.		1 (1.8%)	[severe]
Anxiety	.		1 (1.8%)	[moderate]
Muscle contractions involuntary	.		1 (1.8%)	[moderate]
Status epilepticus	1 (1.9%)	[severe]		
Total	**2 (3.7%)**		**6 (10.9%)**	

Abbreviations: ID, identification; SAE, serious adverse event
(PMA cross-reference: Table 12.4-C, Volume 5)

Table 25: Number of subjects with a serious adverse event by system organ class and phase

System Organ Class	Baseline (3 months) n=157 (Safety – all enrolled data set)	Operative through Unblinded Phases (13 months) n=110 (Safety – all implanted data set)	Long Term Follow-up (3 to 44 months) n=105 (Safety – Long-term Follow-up data set)
Infections and infestations	1 (0.6%)	9 (8.2%)	4 (3.8%)
Metabolism and nutrition disorders			3 (2.9%)
Psychiatric disorders	3 (1.9%)	5 (4.5%)	6 (5.7%)
Nervous system disorders	1 (0.6%)	12 (10.9%)	11 (10.5%)
Respiratory, thoracic and mediastinal disorders	1 (0.6%)		1 (1.0%)
Gastrointestinal disorders		3 (2.7%)	
Musculoskeletal and connective tissue disorders			1 (1.0%)
Renal and urinary disorders		1 (0.9%)	
Pregnancy, puerperium and perinatal conditions			1 (1.0%)
General disorders and administration site conditions	1 (0.6%)	2 (1.8%)	6 (5.7%)
Injury, poisoning and procedural complications	4 (2.5%)	6 (5.5%)	3 (2.9%)
Surgical and medical procedures		1 (0.9%)	
Medtronic		10 (9.1%)	1 (1.0%)
Total [b]	11 (7.0%)	40 (36.4%)	30 (28.6%)

[a] System Organ Class used to group verbatim terms related to diagnostic testing, procedures, imaging, histopathology, or other analyses.
[b] Columns may not add to total as subjects may have experienced more than one event.
(PMA cross-reference: Table 12.4-E, Volume 5, and 90-Day Update)

Table 26: Adverse events occurring in >5% of subjects in either the active or control group during the Blinded Phase, ordered by difference between groups (Safety – all randomized data set)

Preferred term	Active		Control		Difference [a]
	Number of subjects	% (n=54)	Number of subjects	% (n=55)	
Depression	8	14.8%	1	1.8%	13.0%
Memory impairment	7	13.0%	1	1.8%	11.1%
Confusional state	4	7.4%	.	.	7.4%
Anxiety	5	9.3%	1	1.8%	7.4%
Paraesthesia	5	9.3%	2	3.6%	5.6%
Influenza	3	5.6%	.	.	5.6%
Partial seizures with secondary generalization	5	9.3%	3	5.5%	3.8%
Complex partial seizures	5	9.3%	4	7.3%	2.0%
Simple partial seizures	3	5.6%	1	1.8%	3.7%
Anticonvulsant toxicity	3	5.6%	4	7.3%	-1.7%
Dizziness	3	5.6%	4	7.3%	-1.7%
Headache	2	3.7%	3	5.5%	-1.8%
Excoriation	1	1.9%	3	5.5%	-3.6%
Contusion	1	1.9%	4	7.3%	-5.4%
Nasopharyngitis	1	1.9%	5	9.1%	-7.2%
Upper respiratory tract infection	.	.	4	7.3%	-7.3%
Injury	1	1.9%	6	10.9%	-9.1%

[a] Positive = more frequent in the active group; negative = more frequent in the control group.
(PMA cross-reference: Table 12.3-A, Volume 5)

Table 27: Seizure adverse events in either the active or control group during the Blinded Phase, ordered by difference between groups with subject IDs (Safety – all randomized data set)

Preferred term	Active		Control			
	No. of subjects with event	% of subjects (n=54)	No. of subjects with event	% of subjects (n=55)	Difference	p-value
Partial seizures with secondary generalization	5	9.3%	3	5.5%	3.8%	0.4890
Complex partial seizures	5	9.3%	4	7.3%	2.0%	0.7420
Simple partial seizures	3	5.6%	1	1.8%	1.9%	0.3634
Status epilepticus	1	1.9%	.	.	1.9%	0.4954

Table 28: Listing of subjects with Blinded Phase depression adverse events

Medical history of depression?	Event classification	Serious?	Severity	Intervention [a]	Date of event (last visit before event started) [b]	Outcome	Blinded Phase % seizure change from baseline
Active Group (n=8)							
Yes	New Illness/ Injury	No	Mild	Counseling/ therapy, medication	1-Feb-07 (wk 6 on 25-Jan-07)	Ongoing	-94.8%
Yes	Pre-exist Condition	No	Moderate	None [c]	18-Oct-04 (wk 6 on 13-Oct-04)	Resolved (in 15 days)	8.5%
Yes	Pre-exist Condition	Yes: Hosp x2	Moderate	Medication	23-Jul-04 (mo 2 on 13-Jul-04)	Ongoing	-35.1%
Yes	Pre-exist Condition	No	Mild	Medication	17-Dec-04 (wk 6 on 17-Dec-04)	Ongoing	-8.8%
Yes	Pre-exist Condition	No	Mild	None	1-Jun-05 (mo 2 on 27-May-05)	Resolved (in 128 days)	-59.6%
Yes	Pre-exist Condition	No	Moderate	None	16-Jul-04 (wk 6 on 16-Jul-04)	Resolved (in 14 days)	-53.9%
Yes	Pre-exist Condition [d]	No	Moderate	Medication	17-Jan-06 (mo 2 on 17-Jan-06)	Ongoing	-67.7%
No	Programming/ Stimulation	No	Moderate	Counseling/ therapy, reprogramming [e]	27-Oct-04 (wk 4 on 25-Oct-04)	Resolved (in 145 days)	-0.8%
Control Group (n=1)							
No [f]	New Illness/ Injury	No	Mild	Referred to psychiatrist, medication	23-May-07 (mo 2 on 23-May-07)	Ongoing	13.6%

Abbreviations: chg, change; mo, month; wk, week.

[a] Interventions have been summarized as either counseling/therapy, medication, or reprogramming.

[b] Randomization occurred at week 4.

[c] Subject was referred to a psychiatrist, but chose not to be seen.

[d] Subject also reported suicide ideation during the Blinded Phase, which is reported as a separate event.

[e] Reprogramming occurred on several different visits, including voltage changes, turning off 2 of the active contacts. Event resolved after stimulation was turned to a low voltage, bipolar, unilateral configuration.

[f] Subject has a history of 2 suicide attempts at age 17, but no diagnosis of depression.

(PMA cross-reference: Table 12.3-B, Volume 5)

Table 29: Blinded Phase POMS-D scores

	Active group (n=54)			Control group (n=45)			
Test	**Baseline mean ± std.**	**Month 4 mean ± std.**	**Change mean ± std.**	**Baseline mean ± std.**	**Month 4 mean ± std.**	**Change mean ± std.**	**Wilcoxon p-value**
POMS-D T-score a	57.2 ± 12.4	57.9 ± 12.3	0.7 ± 9.3	54.6 ± 10.6	54.2 ± 10.0	-0.5 ± 7.4	0.396

Abbreviations: POMS-D, Profile of Mood States depression subscale; std, standard deviation.
Lower scores indicate better function.
T scores have mean=50 and standard deviation=10.
[a] Excerpt from Section 11.4.5.4, Table 11.4-Z of the PMA (see depression T score).
(PMA cross-reference: Table 12.3-C, Volume 5)

Table 30: Listing of subjects with Blinded Phase memory impairment adverse events

History of memory impairment (previous resective surgeries)	Event classification	Verbatim	Severity	Intervention [a]	Date of event [b]	Outcome
Active Group (n=7)						
Yes (2 previous occipital resections)	Pre-existing condition	Memory impairment	Mild	None	27-Sep-04 (wk 4 on 27-Sep-04)	Resolved (in 15 days)
No (right parieto-occipital topectomy)	Programming/ Stimulation	Memory disruption	Moderate	None	27-Oct-04 (wk 4 on 27-Oct-04)	Resolved (in 12 days)
No (none)	Programming/ Stimulation	Occasional memory lapses since programming @ 4 wk visit	Mild	None	15-Mar-07 (wk 4 on 15-Mar-07)	Resolved (in 61 days)
No (none)	New Illness / Injury	Difficulty with Memory / recalling accuracy of short-term memory	Mild	None	17-Apr-06 (wk 4 on 17-Apr-06)	Resolved (in 126 days)
Yes (none)	Pre-existing Condition	Impaired short-term memory	Moderate	Reprogramming on 2/6/06 and 2/21/06	20-Dec-05 (wk 4 on 20-Dec-05)	Resolved (in 476 days)
No (none)	New Illness / Injury	Short term memory impairment	Mild	None	12-May-05 (wk 6 on 12-May-05)	Resolved (in 14 days)
No (none)	Programming/ Stimulation	Short term memory impairment (forgetfulness, trouble remembering things)	Moderate	Reprogramming on 8/17/06 [c]	3-Aug-06 (wk 4 on 3-Aug-06)	Resolved (in 17 days)
Control Group (n=1)						
No (none)	New Illness/Injury	Worsening memory	Mild	None	1-Jan-05 (mo 2 on 28-Dec-04)	Resolved (in 147 days)

Abbreviations: AE, adverse event; CRF, case report form; mo, month; wk, week
[a] Programming interventions have been summarized. Details of the reprogramming interventions are provided in appendix 16.4.11.1.
[b] Randomization occurred at the week 4 visit.
[c] Date of reprogramming for subject (b) (4) was not reported on an AE CRF, but was reported on the Neurostimulator Interrogation/Programming CRF
(PMA cross-reference: Table 12.3-E, Volume 5)

Table 31: Blinded Phase neuropsychological results by treatment group (Intent-to-treat [Blinded Phase] data set, with exclusions)

	Active group				Control group			
Test	**n**	**Baseline mean ± std.**	**Month 4 mean ± std.**	**Change mean ± std.**	**n**	**Baseline mean ± std.**	**Month 4 mean ± std.**	**Change mean ± std.**
Higher scores indicate better function:								
Attention (ss)	54	6.6 ± 3.8	7.1 ± 4.0	0.7 ± 2.1	46	7.1 ± 3.9	7.3 ± 3.7	0.2 ± 1.8
Executive function (ss)	54	8.8 ± 2.1	9.9 ± 2.4	1.2 ± 1.5	46	8.9 ± 2.8	10.1 ± 2.8	1.2 ± 1.5
Verbal memory (T Score)	54	38.4 ± 12.8	38.0 ± 12.4	-0.4 ± 7.5	46	37.5 ± 13.6	37.4 ± 13.0	-0.1 ± 9.6
Visual memory (T Score)	54	38.6 ± 13.4	37.8 ± 13.3	-0.8 ± 11.7	46	34.3 ± 12.8	36.4 ± 12.2	2.1 ± 11.3
Intelligence	53	95.2 ± 13.0	94.2 ± 14.5	-0.9 ± 7.9	43	93.2 ± 12.1	92.4 ± 13.4	-0.8 ± 8.4
Expressive language (ss)	54	6.3 ± 3.6	5.8 ± 3.3	-0.5 ± 1.8	46	6.1 ± 2.7	5.7 ± 2.7	-0.4 ± 1.6
Lower scores indicate better function:								
Depression (T score)	54	57.2 ± 12.4	57.9 ± 12.3	0.7 ± 9.3	45	54.6 ± 10.6	54.2 ± 10.0	-0.5 ± 7.4
Tension / anxiety (T score)	54	60.0 ± 11.1	58.3 ± 10.7	-1.7 ± 12.1	45	57.3 ± 11.4	54.4 ± 10.2	-2.8 ± 9.3
Total mood disturbance (T score)	54	58.7 ± 9.9	58.2 ± 9.9	-0.5 ± 8.9	45	56.3 ± 10.3	54.9 ± 9.3	-1.4 ± 6.9
Confusion (T score)	54	60.8 ± 11.1	60.2 ± 10.2	-0.7 ± 9.1	45	58.9 ± 12.2	56.8 ± 9.6	-2.1 ± 9.9
Subjective cognitive function (T score)	53	66.5 ± 18.3	62.7 ± 13.9	-3.8 ± 12.8	46	67.3 ± 18.5	63.5 ± 18.8	-3.8 ± 10.5

Abbreviation: std, standard deviation.
Scaled scores (ss) have mean = 10 and standard deviation = 3
T-scores have mean = 50 and standard deviation =10
(PMA cross-reference: Table 11.4-Z Volume 5)

Table 32: Number of subjects with a rescue medication use – Baseline and Blinded Phase, by treatment group (Primary Analysis [Blinded Phase] data set)

Group	N	Baseline	Blinded
Active	54	12 (22%)	12 (22%)
Control	54	12 (22%)	12 (22%)

(PMA cross-reference: Table 11.4-CC, Volume 5)

Table 33: Summary of rescue medication use in the Blinded Phase (Primary Analysis [Blinded Phase] data set)

Group	N	Mean no. of uses	Standard Deviation	Minimum	Median	75th Percentile	Maximum
Active	54	0.79	1.83	0	0	0	10.04
Control	54	2.27	7.59	0	0	0	49.41

Individual subject results were normalized to an 84-day Blinded Phase window.
(PMA cross-reference: Table 11.4-DD, Volume 5)

Table 34: Health care resource utilization in Blinded Phase – by group (Intent-to-treat [Blinded Phase] data set, with exclusions)

	Active Group		Control Group	
Domain	n	Blinded Phase utilization (mean ± std) [a]	n	Blinded Phase utilization (mean ± std) [a]
Hospitalization	54	1.0 (0.02 ± 0.13)	54	4.6 (0.09 ± 0.27)
Emergency room visit	54	1.9 (0.03 ± 0.18)	54	7.0 (0.13 ± 0.39)
Urgent care	54	0.0 (0.00 ± 0.00)	54	0.8 (0.01 ± 0.11)
Day surgery	54	1.8 (0.03 ± 0.17)	54	1.7 (0.03 ± 0.23)
Office/diagnostic visit	54	12.5 (0.23 ± 0.45)	54	13.5 (0.25 ± 0.88)

Abbreviation: std, standard deviation.
[a] Results were normalized to an 84-day Blinded Phase window, thus utilizations are not whole integer numbers.
(PMA cross-reference: Table 11.4-BB Volume 5)

Table 35: Device modifications

	Number of components (Number of subjects)		
Component(s) modified	Explant	Replacement	Revision
Complete system [a]	12 (12)	4 (4)	1 (1)
Neurostimulator	2 (2)	7 (6) [b]	5 (5)
Leads	0 [c]	16 [d] (11)	2 [d] (1)
Extensions	2 (1)	17 (8)	4 (3)

Source: Appendix 16.1.5.2 of the PMA
[a] Neurostimulator, leads, and extensions
[b] An additional 42 neurostimulator replacements occurred in 31 subjects due to battery depletion.
[c] All lead explants occurred as part of a total system explant.
[d] One lead replacement and one lead revision occurred during the initial implant surgery.
(PMA cross-reference: Table 12.5-F, Volume 5)

Table 36: Primary efficacy data sets analyzed

Data Sets Analyzed	Total n	Active n	Control n	Total Excluded
Efficacy data sets, Blinded Phase				**Total excluded from n=109 [a]**
Primary Analysis (Blinded Phase)	108	54	54	1 (66 out of 70 required diary days)
Intent-to-treat (Blinded Phase)	109	54	55	0
Per-protocol (Blinded Phase)	98	46	52	11 (10 subjects with permanent changes to AEDs Baseline through Blinded Phases and 1 with 66 out of 70 required diary days)
As Treated (95%) (Blinded Phase)	89	35	54	20 (4 missing data, 15 subjects with less than 95% usage and 1 with 66 out of 70 required diary days)
As Treated (80%) (Blinded Phase)	100	46	54	9 (4 missing data, 4 subjects with less than 80% usage and 1 with 66 out of 70 required diary days)
"Subject B" Removed (Blinded Phase)	107	54	53	2 (1 with possibly unreliable diary ["B"] and 1 with 66 out of 70 required diary days)
Efficacy data sets, Unblinded Phase				**Total excluded from n=108 [b]**
Unblinded Phase	86	-	-	22 (22 subjects with less than 70 days of diary months 1-4, 4-7, 7-10, and 10-13)
Intent-to-treat (Unblinded Phase)	108	-	-	0
Per-protocol (Unblinded Phase)	71	-	-	37 (Subjects excluded with less than 70 days of diary months 1-4, 4-7, 7-10, and 10-13, and any permanent changes to AEDs in Baseline, Blinded, or Unblinded Phases)
Efficacy data sets, Long-term Follow-up Phase				**Total excluded from n=105 [c]**
Long-term Follow-up Phase	105	-	-	0
Long-term Follow-up Phase – 2 years	100	-	-	5 (3 discontinued, 2 have not reached 2 years of stimulation time)
Long-term Follow-up Phase – 3 years	57	-	-	48 (6 discontinued, 40 not yet due for 3-year visit, 2 have not reached 2 years of stimulation time)

Abbreviations: [-], not relevant; AEDs, antiepileptic drugs; SUDEP, sudden unexplained death in epilepsy.

[a] Of the 110 subjects who received an implant, 109 were randomized to treatment

[b] Of the 109 subjects who were randomized to treatment, 108 entered the Unblinded Phase, one subject skipped to the Long-term Follow-up Phase.

[c] Of the 108 subjects who entered the Unblinded Phase, 5 discontinued in the Unblinded Phase, and two subjects skipped to the Long-term Follow-up Phase.

(PMA cross-reference: Table 11.1-A, Volume 5; Table 6-A of the 90-Day Update)

Table 37: Primary Objective and Sensitivity Analysis

	All Eligible Subjects			"Subject A" Removed		
Analysis Method	**Factors with p < 0.1**	**Treatment Effect Wald p-value**	**Difference Estimate $(e^{\beta}-1)*100$ [95% Confidence Interval] [a]**	**Factors with p < 0.1**	**Treatment Effect Wald p-value**	**Difference Estimate $(e^{\beta}-1)*100$ [95% Confidence Interval][a]**
Primary Analysis Active n=54 Control n=54	Visit, Treatment by visit interaction, Log of age	Overall: 0.483 Month 3-4: 0.0017	Overall: n/a Month 3-4: -29% [-43%, -12%]	Visit, Treatment by visit interaction, Log of age	Overall: 0.043 Month 3-4: 0.0023	Overall: n/a Month 3-4:- 29% [-43%, -11%]
Subj. B. Removed Active n=54 Control n=53	Visit, Treatment by visit interaction, Log of age	Overall: 0.562 Month 3-4: 0.003	Overall: n/a Month 3-4: -28% [-43%, -11%]	Visit, Treatment by visit interaction, Log of age	Overall: 0.063 Month 3-4: 0.003	Overall: n/a Month 3-4: -28% [-42%, -10%]
Intent-to-Treat Active n=54 Control n=55	Visit, Treatment by visit interaction, Log of age	Overall: 0.470 Month 3-4: 0.0016	Overall: n/a Month 3-4: -29% [-43%, -12%]	Visit, Log of age	Overall: 0.039 Month 3-4: 0.0022	Overall: -17% [-31%, -1%] Month 3-4: -29% [-43%, -11%]
Per Protocol Active n=46 Control n=52	Visit	Overall: 0.416 Month 3-4: 0.004	Overall: -11% [-34%, 20%] Month 3-4: -29% [-43%, -10%]	Visit, Log of age	Overall: 0.023 Month 3-4: 0.006	Overall: -21% [-35%, -3%] Month 3-4: -28% [-43%, -8%]
As Treated (95%) Active n=35 Control n=54	Visit, Log of age	Overall: 0.404 Month 3-4: 0.003	Overall: -10% [-42%, 39%] Month 3-4: -32% [-48%, -12%]	Log of age	Overall: 0.004 Month 3-4: 0.003	Overall: -28% [-42%, -10%] Month 3-4: -32% [-48%, -12%]
As Treated (80%) Active n=46 Control n=54	Visit, Log of age	Overall: 0.316 Month 3-4: 0.0006	Overall: -11% [-37%, 25%] Month 3-4: -32% [-45%, -15%]	Log of age	Overall: 0.004 Month 3-4: 0.0008	Overall: -24% [-37%, -8%] Month 3-4: -31% [-45%, -14%]

[b] Overall estimates are provided for models where a treatment by visit interaction is not present.

Table 38: Unadjusted median total seizure frequency percent change from baseline (Primary Analysis [Blinded Phase] data set)

	Active				Control			
Visit	n	Median	25th percentile	75th percentile	n	Median	25th percentile	75th percentile
Baseline	54	0.0%	0.0%	0.0%	54	0.0%	0.0%	0.0%
Operative [a]	53	-21.3%	-42.5%	5.3%	53	-22.2%	-62.7%	9.3%
Month 1-2	54	-33.9%	-59.7%	17.3%	54	-25.3%	-51.7%	13.8%
Month 2-3	54	-42.1%	-61.0%	-19.3%	54	-28.7%	-66.4%	-5.0%
Month 3-4	54	-40.4%	-62.9%	-21.6%	54	-14.5%	-50.3%	20.0%
All Blinded	54	-35.0%	-53.9%	-13.0%	54	-21.1%	-51.5%	7.5%

[a] Operative Phase diary data were not available for 2 subjects (active n=1, control n=1).

Table 39: Median seizure frequency (Primary Analysis [Blinded Phase] data set)

	Active				Control			
	n	Median	25th percentile	75th percentile	n	Median	25th percentile	75th percentile
Baseline	54	18.4	9.9	53.7	54	20.2	10.3	46.5
Operative	53	-3.3	-12.2	2.1	53	-3.3	-14	3
Month 1-2	54	-4.5	-17.1	3.1	54	-4.2	-13.5	3.4
Month 2-3	54	-6.7	-23.8	-2.1	54	-4.5	-16.1	-0.8
Month 3-4	54	-8.5	-18	-4.8	54	-2	-12.1	4.3
All Blinded	54	-5.2	-19.2	-1.8	54	-2.9	-11.3	1.4

Table 40: Blinding Assessment – Subject responses at study week 6 and month 4

Subject response	Treatment assignment	
	Active	Control
Week 6 visit		
Correct	25 (47.2%)	16 (30.8%)
Incorrect	10 (18.9%)	12 (23.1%)
Does not know	18 (34%)	24 (46.2%)
Total	53	52
Month 4 visit		
Correct	24 (44.4%)	21 (40.4%)
Incorrect	14 (25.9%)	12 (23.1%)
Does not know	16 (29.6%)	19 (36.5%)
Total	54	52

(PMA cross-reference: Table 11.4-E, Volume 5)

Table 41: Seizure distribution over time (unadjusted) (Primary Analysis [Blinded Phase] data set)

	Active				Control			
Visit	n	Median	25th percentile	75th percentile	n	Median	25th percentile	75th percentile
Week -12 to -8	54	18.6	11.5	50.2	54	23.6	10.0	55.0
Week -8 to -4	54	15.0	9.6	59.0	54	21.7	10.0	48.1
Week -4 to 0	54	19.9	10.2	56.0	54	17.3	9.0	49.0
Month 1-2	54	16.9	6.7	32.7	54	16.8	8.3	40.0
Month 2-3	54	12.4	5.0	33.2	54	14.8	5.6	32.0
Month 3-4	54	11.6	4.0	30.6	54	17.2	7.5	37.3

Table 42: Median total seizure frequency % change from baseline (entire Blinded Phase) by age

Age Category	Active	Control
< 36 (median)	-36.2% (n=29)	-13.3% (n=25)
≥ 36 (median)	-35.0% (n=25)	-27.0% (n=29)
< 45 (75th quartile)	-35.0% (n=41)	-13.7% (n=40)
≥ 45 (75th quartile)	-35.0% (n=13)	-41.2% (n=14)

Table 43: Responder rate over the Blinded Phase (Primary Analysis [Blinded Phase] data set)

Group	No. of responders	Total n	% responder	Fisher's Exact p-value
Active	16	54	29.6%	0.830
Control	14	54	25.9%	

(PMA cross-reference: Table 11.4-J, Volume 5)

Table 44: Seizure-free days over the Blinded Phase (Primary Analysis [Blinded Phase] data set)

Group	N	Baseline mean ± std.	Blinded mean ± std.	% Change mean ± std.	Median % change	Wilcoxon p-value
Active	50	46.7 ± 20.9	57.3 ± 20.0	124.7% ± 446.1%	15.3%	0.105
Control	50	44.5 ± 23.5	51.7 ± 24.5	60.1% ± 208.4%	8.8%	

Abbreviation: std, standard deviation.
(PMA cross-reference: Table 11.4-K, Volume 5)

Table 45: Maximum length of seizure-free intervals over the Blinded Phase (Primary Analysis [Blinded Phase] data set)

Group	N	Baseline mean ± std. (days)	Blinded mean ± std. (days)	% Change mean ± std.	Median % change	Wilcoxon p-value
Active	54	8.0 ± 4.5	11.9 ± 8.9	60.6% ± 97.6%	35.0%	0.498
Control	54	8.7 ± 6.2	11.9 ± 10.6	55.8% ± 120.6%	24.0%	

Abbreviation: std, standard deviation.
(PMA cross-reference: Table 11.4-L, Volume 5)

Table 46: Mean and Median a Seizure Frequency and % Change From Baseline by Seizure Type

Seizure Type	Group	n	Baseline mean ± std.	Baseline median	Operative Median	Blinded mean ± std.	Blinded median	% Change mean ± std.	Median % change	Min to Max change
Simple partial	Active	37	53.7 ± 116.5	7.8	6.3	39.4 ± 90.5	5.9	-26.6% ± 76.4%	-39.9%	-100% to 322.2%
	Control	32	26.7 ± 47.6	9.6	7.6	24.3 ± 55.0	6.6	-26.1% ± 59.3%	-38.5%	-100% to 133.3%
Complex partial	Active	48	22.0 ± 30.6	10.4	8.1	17.0 ± 28.1	4.0	-4.2% ± 146.9%	-36.3%	-100% to 822%
	Control	49	28.7 ± 52.5	11.3	8.7	30.3 ± 73.6	9.3	-9.3% ± 47.7%	-12.1%	-100% to 112.6%
Partial to generalized	Active	19	2.6 ± 2.9	1.3	0	1.8 ± 2.3	1.0	6.2% ± 149.1%	-48.2%	-100% to 435.7%
	Control	21	7.6 ± 17.0	3.3	1.2	5.3 ± 14.2	1.7	-22.4% ± 61.3%	-24.7%	-100% to 142%
Most severe [b]	Active	54	10.0 ± 17.9	4.0	1.7	5.9 ± 15.3	1.6	-14.2% ± 87.9%	-24.7%	-100% to 435.7%
	Control	54	20.4 ± 50.7	3.8	1.3	20.6 ± 66.5	1.7	-7.3% ± 49.7%	0%	-100% to 142%
Most severe [c]	Active	43	12.6 ± 19.3	6.6	2.9	7.3 ± 16.8	2.3	-27.1% ± 91.2%	-39.6%	-100% to 435.7%
	Control	38	28.9 ± 58.5	7.5	4.3	29.2 ± 78.0	5.3	-13.0% ± 56.3%	-20.4%	-100% to 142%

[a] Means and medians are calculated on a per 28 diary day basis.

[b] If a subject did not have a 'Most Severe' seizure at baseline, then the % Change was calculated as 0% if there were no 'Most Severe' seizures in the phase, and 100% if the number of 'Most Severe' seizures in the phase was greater than 0.

[c] If a subject did not have a 'Most Severe' seizure at baseline they are not included in the analysis (i.e., "protocol-specified" analysis).

Table 47: Liverpool Seizure Severity-Blinded Phase (Intent-to-treat [Blinded Phase] data set, with exclusions)

Group	n	Baseline mean ± std.	Blinded mean ± std.	Change mean ± std.	Median change	Minimum to maximum change
Active	53	48.7 ± 17.9	40.4 ± 20.1	-8.2 ± 17.8	-2.5	-67.5 to 15
Control	53	50.5 ± 18.1	43.7 ± 19.1	-6.8 ± 19.6	-5.0	-85 to 50

(PMA cross-reference: Table 11.4-Q Volume 5)

Table 48: Access Therapy Controller use (Primary Analysis [Blinded Phase] data set, with exclusions)

Group	n	Blinded mean ± std.	Blinded median	Minimum to maximum change
Active	49	36.3 ± 72.6	13.0	0 to 352
Control	48	69.9 ± 139.7	16.0	0 to 788

(PMA cross-reference: Table 11.4-S Volume 5)

Table 49: QOLIE-31 Scores – Blinded Phase primary QOLIE analysis (Intent-to-treat [Blinded Phase] data set, with exclusions)

	Active group				Control group			
Domain	n	Baseline T-score mean ± std.	Month 4 T-score mean ± std.	Change in T-score mean ± std.	n	Baseline T-score mean ± std.	Month 4 T-score mean ± std.	Change in T-score mean ± std.
Seizure worry	53	45.1±9.2	47.6±9.8	2.5±9.8	53	45.8±9.7	49.3±11.2	3.5±10.5
Overall quality of life	53	44.3±8.7	46.0±9.6	1.7±10.2	53	46.1±9.5	48.6±8.0	2.5±8.5
Emotional well-being	52	47.4±9.4	48.4±9.6	1.1±6.9	53	50.0±7.7	52.0±8.3	1.9±8.1
Energy / Fatigue	52	45.8±9.1	48.1±8.5	2.3±9.3	53	47.8±7.9	48.8±8.2	1.0±8.6
Cognitive functioning	53	45.6±9.7	45.9±10.6	0.2±9.4	53	46.1±10.2	47.3±10.6	1.2±8.6
Medication effects	53	48.1±9.7	49.8±10.7	1.7±9.4	53	48.1±9.3	50.0±9.7	2.0±9.0
Social functioning	53	39.1±8.2	41.7±8.8	2.7±9.8	53	40.0±9.9	42.7±9.0	2.7±7.8
Overall score	52	41.8±8.6	44.3±9.6	2.5±8.7	53	43.4±9.4	46.2±10.0	2.8±8.0

Abbreviation: std, standard deviation.
(PMA cross-reference: Table 11.4-T Volume 5)

Table 50: Satisfaction with therapy (Intent-to-treat [Blinded and Unblinded Phases] data set, with exclusions)

		Very satisfied		Somewhat satisfied		Neutral		Somewhat dissatisfied		Not satisfied	
Group or visit	Number of subjects	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Active Month 4	54	18	33.3%	12	22.2%	17	31.5%	5	9.3%	2	3.7%
Control Month 4	52	14	26.9%	22	42.3%	13	25.0%	0	0.0%	3	5.8%
Month 7	106	44	41.5%	36	34.0%	15	14.2%	5	4.7%	6	5.7%
Month 10	99	41	41.4%	35	35.4%	14	14.1%	5	5.1%	4	4.0%
Month 13	100	44	44.0%	30	30.0%	18	18.0%	4	4.0%	4	4.0%

(PMA cross-reference: Table 11.4-V Volume 5)

Table 51: Therapy recommendation (Intent-to-treat [Blinded and Unblinded Phases] data set, with exclusions)

	Go through again for same result?		Would recommend to a friend?	
Group or visit	Yes / n [a]	(%)	Yes / n [a]	(%)
Active month 4	36 / 53	67.9%	43 / 54	79.6%
Control month 4	42 / 53	79.2%	48 / 53	90.6%
Month 7	86 / 105	81.9%	90 / 107	84.1%
Month 10	82 / 100	82.0%	85 / 99	85.9%
Month 13	81 / 100	81.0%	89 / 101	88.1%

[a] Indicates number of subjects and not a "No" answer

(PMA cross-reference: Table 11.4-W Volume 5)

Table 52: Outcome variables – Month 4 (Intent-to-treat [Blinded Phase] data set, with exclusions)

	Active (n=54)				Control (n=54)			
	Baseline		Month 4		Baseline		Month 4	
Outcome variable	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Employment status								
Currently employed full time	7	13%	7	13%	8	15%	9	17%
Currently employed part time	7	13%	5	9%	7	13%	6	11%
Unemployed, able to work	2	4%	5	9%	0	0%	0	0%
Unemployed due to epilepsy	30	56%	30	56%	35	65%	36	67%
Unemployed due to a disability other than epilepsy	3	6%	2	4%	2	4%	1	2%
Retired	0	0%	0	0%	0	0%	0	0%
Homemaker	0	0%	0	0%	0	0%	0	0%
Student, full time	7	13%	3	6%	2	4%	1	2%
Student part time	2	4%	2	4%	0	0%	1	2%
Sheltered/supported employment	1	2%	0	0%	2	4%	1	2%
Driving status								
Valid drivers license and driving a motor vehicle	5	9%	2	4%	1	2%	2	4%
Valid drivers license but not driving a motor vehicle	6	11%	9	17%	10	19%	5	9%
No valid drivers license due to epilepsy	43	80%	42	78%	42	78%	46	85%
No valid drivers license, other reason	0	0%	0	0%	1	2%	1	2%
Participant prefers not to answer question	0	0%	1	2%	0	0%	0	0%
Other	0	0%	0	0%	0	0%	0	0%
Living arrangements								
Living alone	4	7%	5	9%	5	9%	6	11%
Living with family	44	81%	44	81%	45	83%	45	83%
Living with non-family (not a group setting)	5	9%	4	7%	2	4%	2	4%
Nursing home, assisted living or other group setting	1	2%	1	2%	0	0%	0	0%
Other	0	0%	0	0%	2	4%	1	2%
Primary caregiver								
No	34	63%	37	69%	39	72%	38	70%
Yes	20	37%	17	31%	15	28%	16	30%
Wife or husband	2	4%	3	6%	8	15%	9	17%
Children	1	2%	0	0%	0	0%	0	0%
Friend	1	2%	1	2%	0	0%	0	0%
Parents (or in-laws)	15	28%	10	19%	7	13%	7	13%
Other	1	2%	3	6%	0	0%	0	0%

(PMA cross-reference: Table 11.4-X Volume 5)

11. Figures

I. Partial seizures (Focal Seizures)
- A. Simple partial seizures
  - □ 1. with motor signs
  - □ 2. with somatosensory or special sensory symptoms
  - □ 3. with autonomic symptoms or signs
  - □ 4. with psychic symptoms
- B. Complex partial seizures
  - □ 1. simple partial onset followed by impairment of consciousness
  - □ 2. with impairment of consciousness at the onset
- C. Partial seizures evolving to secondarily generalized seizures
  - □ 1. simple partial seizures (A) evolving to generalized seizures
  - □ 2. complex partial seizures (B) evolving to generalized seizures

□ 3. simple partial seizures evolving to complex partial seizures evolving to generalized seizures

II. Generalized (Convulsive or Nonconvulsive)
- □ A. 1. typical absence seizures (petit mal)
  - □ 2. atypical
- □ B. Myoclonic seizures
- □ C. Clonic seizures
- □ D. Tonic seizures
- □ E. Tonic-clonic seizures (grand-mal)
- □ F. Atonic seizures

□ **III. Unclassified Epileptic Seizures**

□ **IV. Status Epilepticus**

□ Other, specify:_____

Figure 1: ILEA Seizure Classification

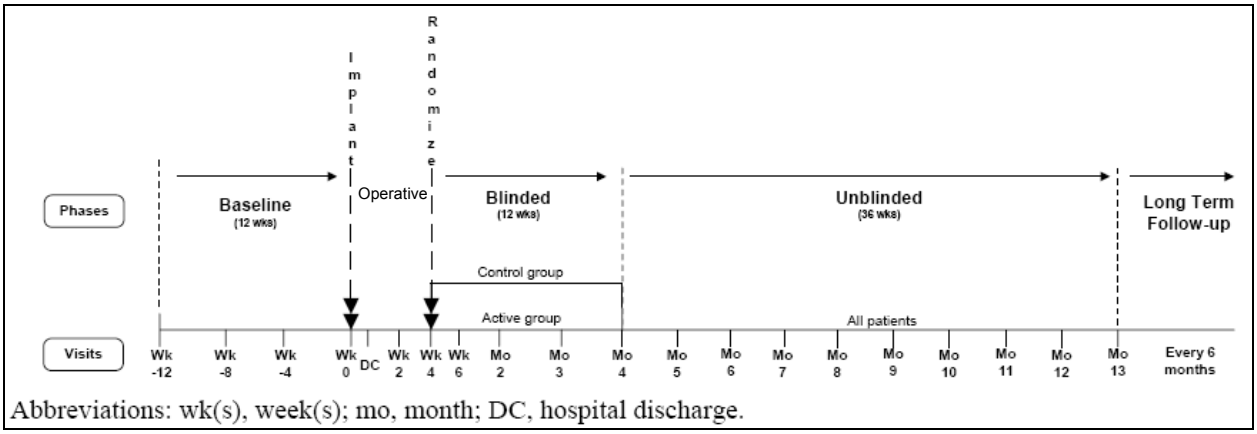
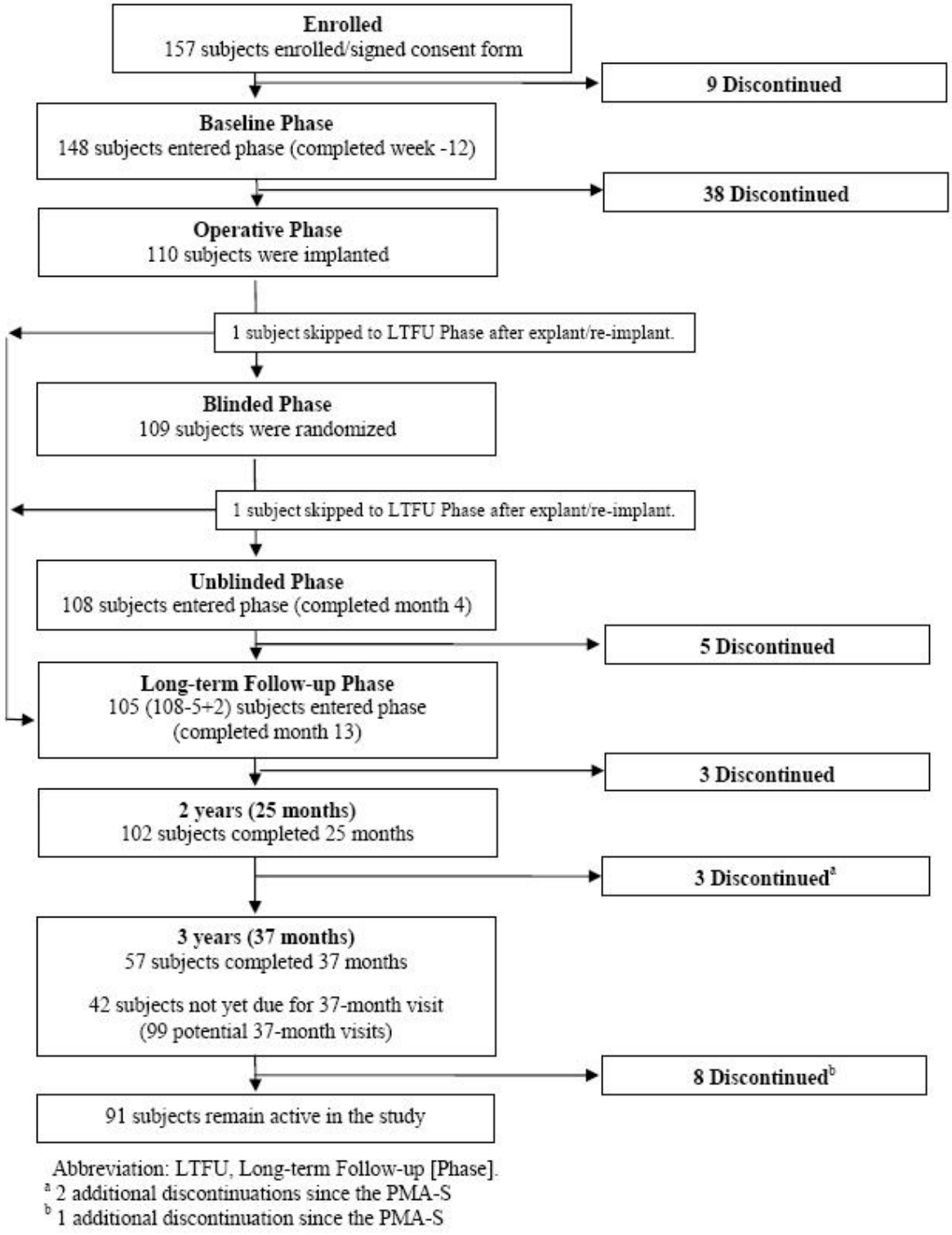


Figure 2: Study Design Schema



Abbreviation: LTFU, Long-term Follow-up [Phase].
[a] 2 additional discontinuations since the PMA-S
[b] 1 additional discontinuation since the PMA-S

Figure 3: Accountability

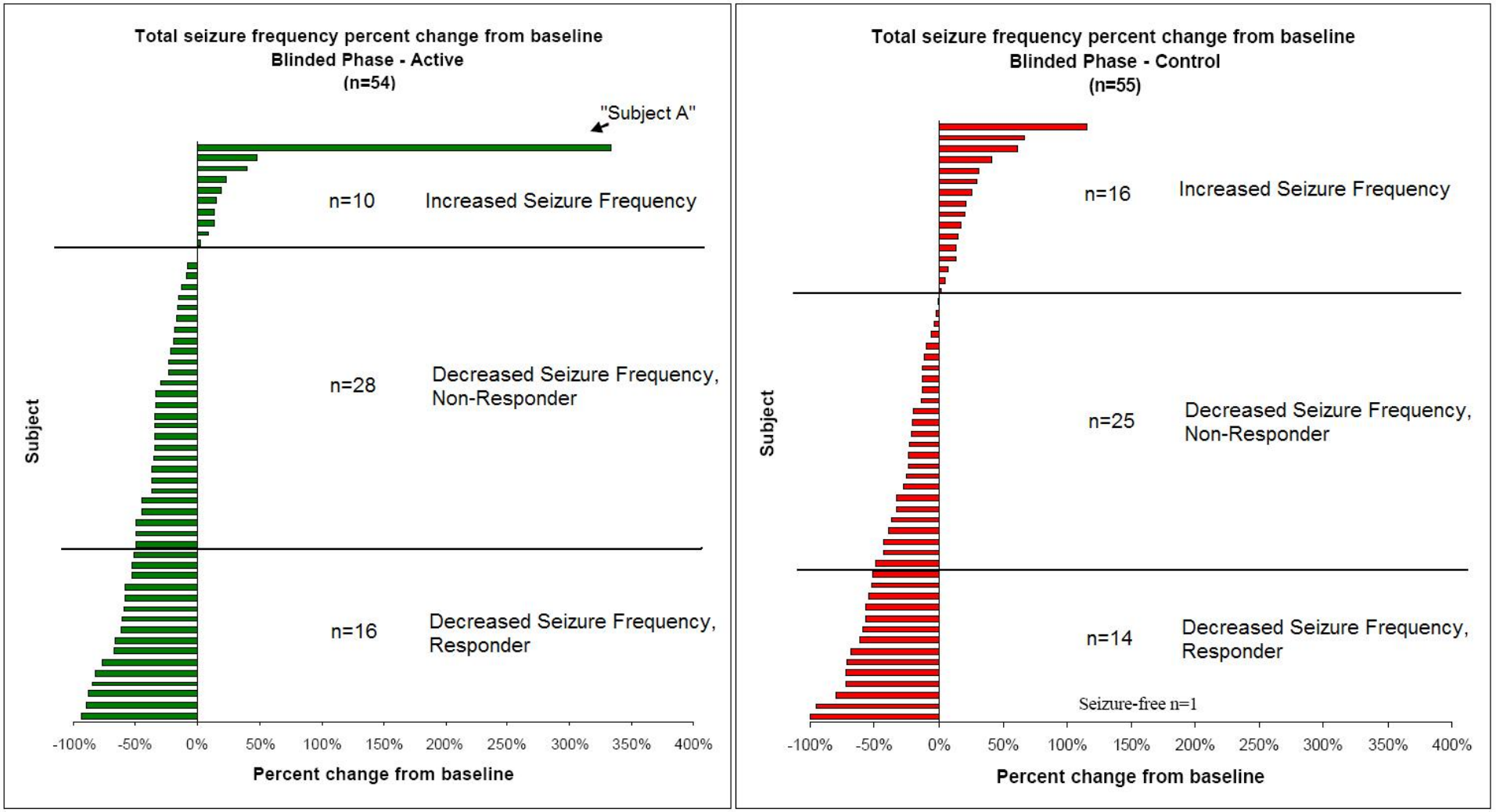


Figure 4: Total seizure frequency percent change from baseline –Blinded Phase

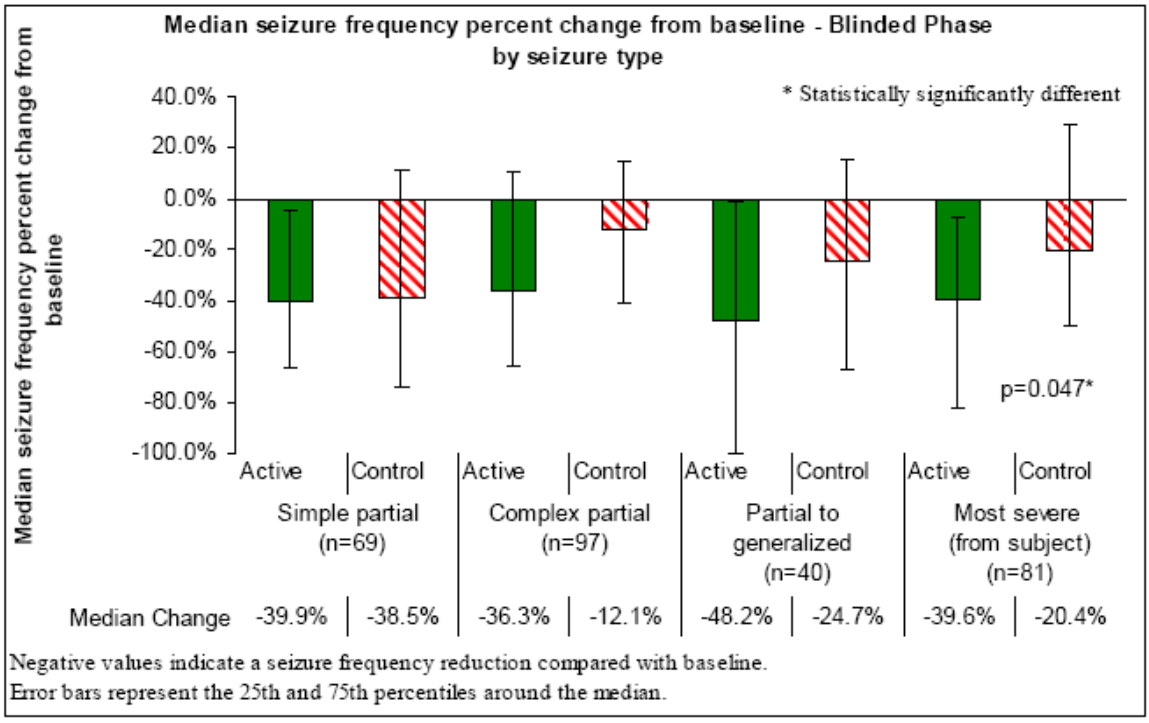


Figure 5: Median total seizure frequency percent change from baseline by seizure type – Blinded Phase (Primary Analysis [Blinded Phase] data set)

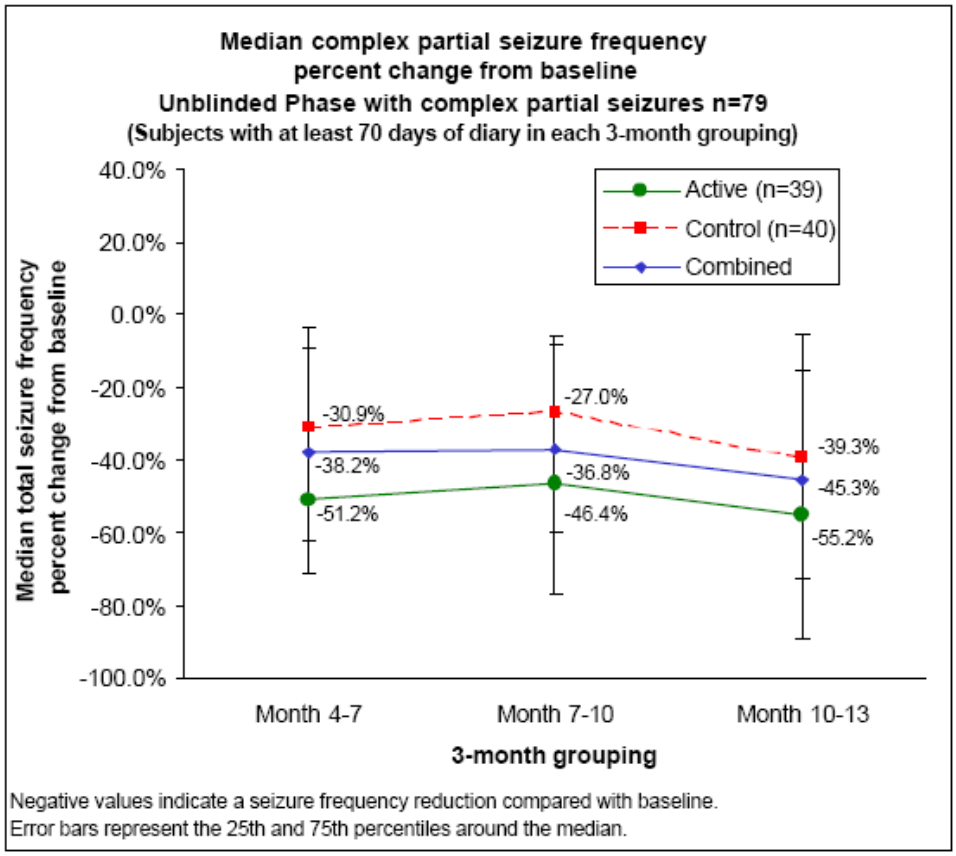


Figure 6: Median complex partial seizure frequency percent change from baseline – Unblinded Phase

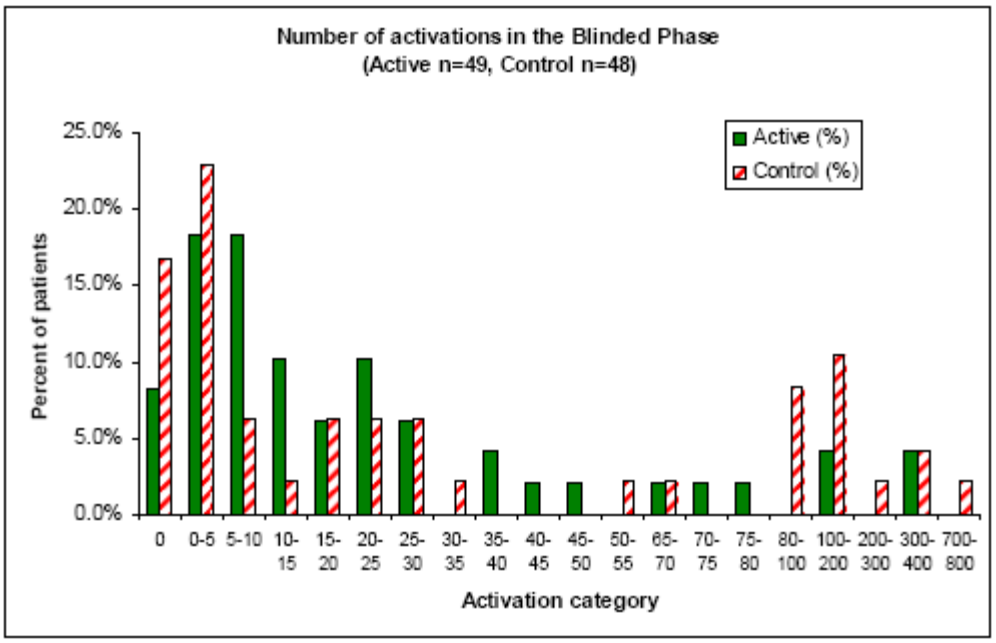


Figure 7: Access Therapy Controller activation distribution
(Primary Analysis [Blinded Phase] data set, with exclusions)

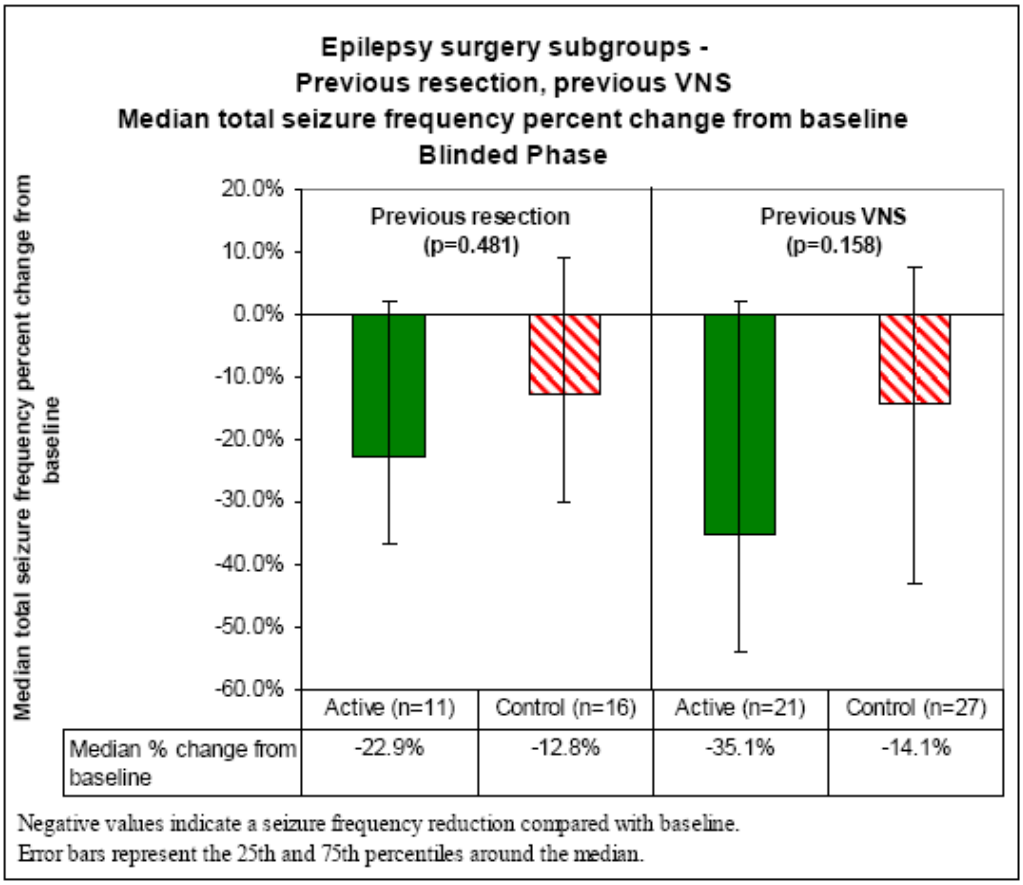


Figure 8: Effect of previous resection, previous VNS – Blinded Phase
(Primary Analysis [Blinded Phase] data set)
Abbreviations: VNS, vagus nerve stimulation/stimulator

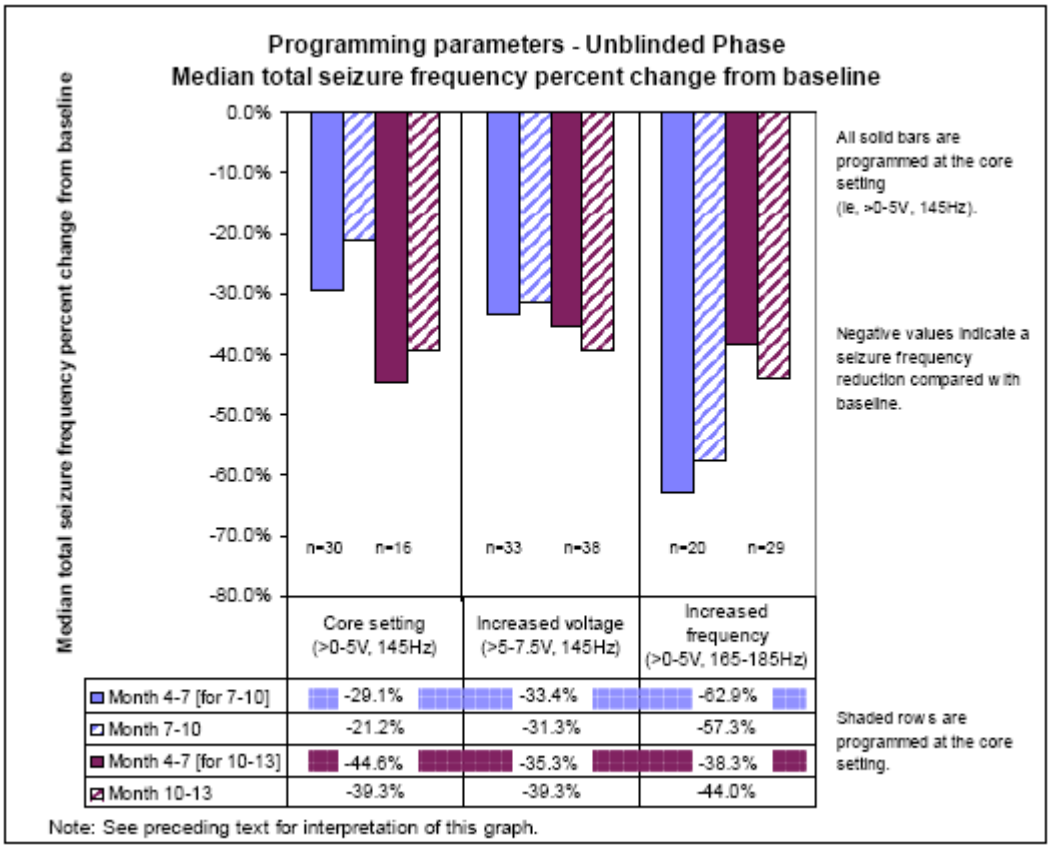


Figure 9: Results by change in programming parameters - Unblinded phase (Unblinded phase data set)

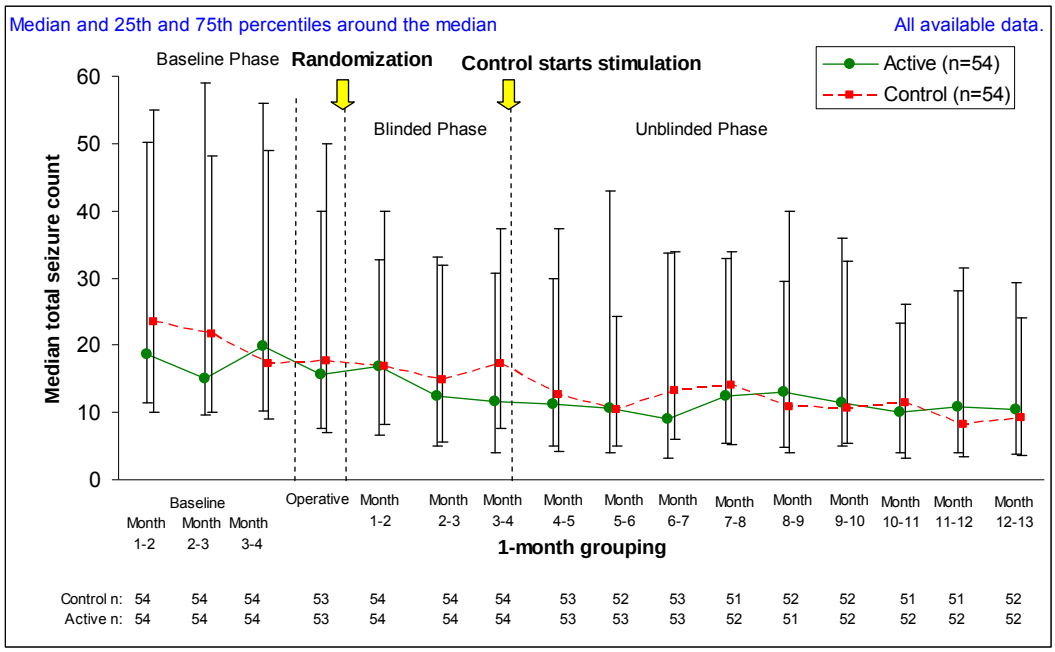


Figure 10: Month-to-month median total seizure frequency percent change from baseline